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DECLARATION

I, Yoshiaki TODAKA of c/o The Patent Corporate Body ARUGA PATENT OFFICE, 3-6, Nihonbashiningyocho 1-chome, Chuo-ku, Tokyo 103-0013 Japan do solemnly and sincerely declare that I well understand both Japanese and English languages and that I believe the attached English version is a true and complete translation of the Japanese Patent Application No. 10-244175 filed on August 28, 1998 in the name of Daiichi Pharmaceutical Co., Ltd.

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【Document Name】 Specification 1
【Document Name】 Abstract 1

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【Request of Identification of Data】 Requested

[Document Name] SPECIFICATION

[Title of the Invention] NOVEL SULFONYL DERIVATIVES

[Claims]

[Claim 1] A sulfonyl derivative represented by the following formula (I):

[Chemical formula 1]

$$Q^1-Q^2-T^1-Q^3-SO_2-Q^A \qquad (I)$$

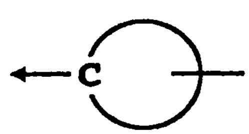
[wherein Q^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent,

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} alkynylene group,

a group $-N(R^1)-CO-$ (in which R^1 represents a hydrogen atom or an alkyl group),

a group $-N(R^2)-(CH_2)_m-$ (in which R^2 represents a hydrogen atom or an alkyl group and m stands for an integer of 0 to 6), or a group of the following formula:

[Chemical formula 2]



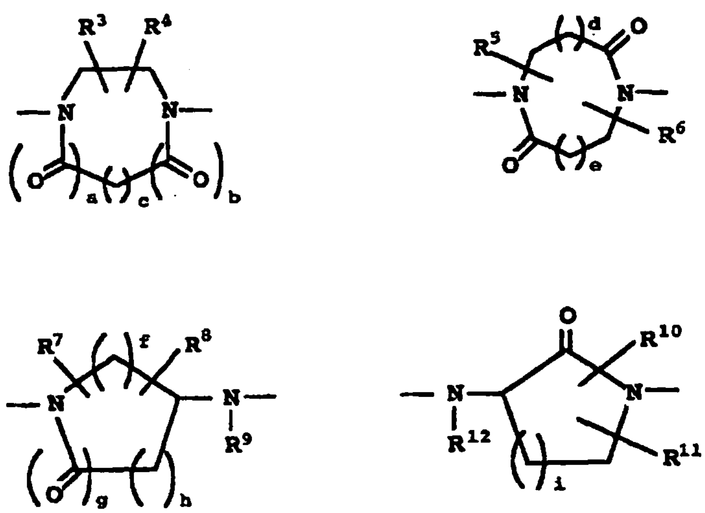
(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, or

a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and ←C means the bonding of the carbon atom of this group to Q^1),

Q^3 represents any one of the following groups:

[Chemical formula 3]



(in which, when the carbon atom to which each of R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} has been bonded is not adjacent to a nitrogen atom, R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} each independently represents a hydrogen atom,

a hydroxyl group,

an alkyl group,

an alkoxyl group,

an alkoxyalkyl group,

an alkoxyalkyloxy group,

a hydroxyalkyl group,

a hydroxyalkyloxy group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylsulfonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonylalkyl group,

a carboxyl group,

a carboxyalkyl group,

a carboxyalkyloxy group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkyloxy group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an amino group which may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents or

a group A^1-B^1- (in which A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^1 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group -NHCO or a group -NHCO-(C_{1-6} alkylene) group),

when the carbon atom to which each of R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} has been bonded is adjacent to a nitrogen

atom, R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} each independently represents

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylsulfonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonylalkyl group,

a carboxyl group,

a carboxyalkyl group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxyalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or

a group A^2-B^2- (in which A^2 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, and B^2 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group -NHCO or a group -NHCO-(C_{1-6} alkylene) group),

each of R^3 and R^4, R^5 and R^6, R^7 and R^8, and R^{10} and R^{11} may be coupled together with a carbon atom which constitutes the ring and represent a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

R^9 and R^{12} each independently represents:

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

an alkoxyl group,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

a carboxyalkyl group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an amino group which may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxycarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or

an aminocarbonyloxyalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

R^9 and R^7 or R^8 may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^9 has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

R^{12} and R^{10} or R^{11} may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^{12} has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

a, b, d, e and g each independently stands for an integer of 0 or 1, c stands for an integer of 0 to 3, and f,

h and i each independently represents an integer of 1 to 3, with the proviso that the sum of a, b and c stands for an integer of 2 or 3, the sum of d and e stands for an integer of 0 or 1 and the sum of f, g and h stands for an integer of 3 to 5),

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group Ar-C(H)=N- (in which, Ar represents an aryl group which may have a substituent), or a group Het-C(H)=N- (in which, Het represents a heteroaryl group which may have a substituent), and

T^1 represents a carbonyl group,

a group $-CH(R^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group having the hydroxyl group which may be protected, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent (protecting group)), or

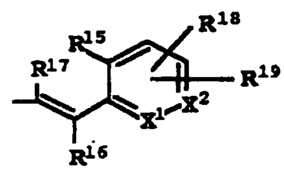
a group $-C(=NOR^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group,

an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent)], or salt thereof; or a solvate thereof.

[Claim 2] A sulfonyl derivative according to claim 1, wherein in the formula (I), Q^A represents any one of the below-described groups:

[Chemical formula 4]



[wherein R^{15} represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, a halogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyl group, an alkoxyalkyl group, a carboxyl group, a carboxyalkyl group, an alkylcarbonyl group, an alkoxycarbonyl group, an alkoxycarbonylalkyl group, an alkylcarbonyloxy group or a group A^3-B^3-

(wherein A^3 represents an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^3 represents a single bond, a carbonyl group, an alkylene group, a carbony-

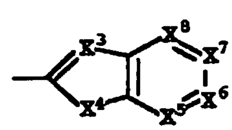
lalkyl group, a carbonylalkyloxy group or an alkylenecarbonyloxy group),

R^{16} and R^{17} each independently represents a hydrogen atom, a halogen atom, an alkyl group, a hydroxyalkyl group having a hydroxyl group which may be protected or an alkoxyalkyl group, or R^{16} or R^{17} may be coupled together with R^{15} and represent a C_{1-3} alkylene or alkenylene group,

R^{18} and R^{19} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a trifluoromethyl group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the proviso that R^{18} and R^{19} do not represent a hydrogen atom at the same time), and

X^1 and X^2 each independently represents a methine group or a nitrogen atom].

[Chemical formula 5]



[wherein X^3 represents a nitrogen atom, or

a group $=C(R^{100})-$

(wherein R^{100} represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxycarbonyl group, an aralkyloxycarbonylalkyl group, an alkoxycarbonylalkyl group, a nitro group, an amino group which may have a protecting group or an aminoalkyl group which may have, at the amino moiety thereof, a protecting group),

X^4 represents an oxygen atom, a sulfur atom or a group $-N(R^{101})-$

(wherein R^{101} means a hydrogen atom, an alkyl group, an alkoxycarbonyl group, an aralkyloxycarbonyl group, an alkoxycarbonylalkyl group, an alkylsulfonyl group or an arylsulfonyl group),

X^5 and X^8 each independently represents a nitrogen atom or a group $-C(R^{102})-$

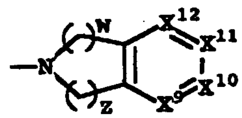
(wherein R^{102} represents a hydrogen atom or a halogen atom),

X^6 and X^7 each independently represents a nitrogen atom or a group $-C(R^{103})-$

(wherein R^{103} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group,

an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group)].

[Chemical formula 6]



[wherein X^9 and X^{12} each independently represents a nitrogen atom or

a group $-C(R^{104})-$

(wherein R^{104} represents a hydrogen atom or a halogen atom),

X^{10} and X^{11} each independently represents a nitrogen atom or

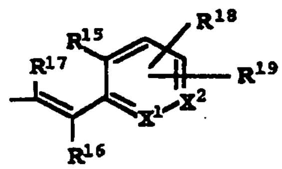
a group $-C(R^{105})-$

(wherein R^{105} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, and

w and z each independently represents an integer of 1 or 2], or salt thereof; or a solvate thereof.

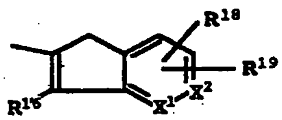
[Claim 3] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 7]



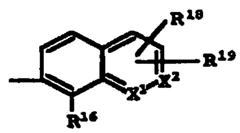
means the following group:

[Chemical formula 8]



or

[Chemical formula 9]

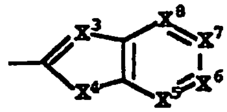


[in the above groups, R^{16}, R^{18}, R^{19}, X^1 and X^2 have the same meanings as defined above], or salt thereof; or a solvate thereof.

[Claim 4] A sulfonyl derivative according to claim 2 or 3, wherein R^{18} represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

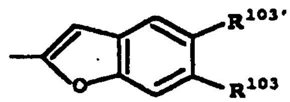
[Claim 5] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 10]

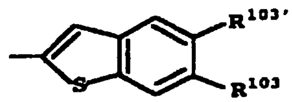


means any one of the following groups:

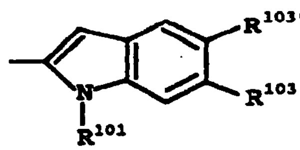
[Chemical formula 11]



[Chemical formula 12]



[Chemical formula 13]

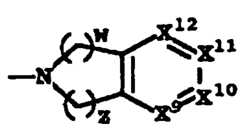


[in the above formulas, R^{101} and R^{103} have the same meanings as defined above and $R^{103'}$ represents similar atoms or groups to R^{103}], or salt thereof; or a solvate thereof.

[Claim 6] A sulfonyl derivative according to claim 5, wherein either one of R^{103} and $R^{103'}$ represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

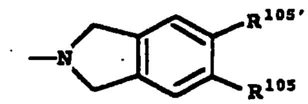
[Claim 7] A sulfonyl derivative according to claim 2, wherein in the formula (I), the group:

[Chemical formula 14]



represents the following group:

[Chemical formula 15]

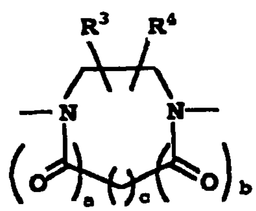


[wherein R^{105} has the same meaning as defined above and $R^{105'}$ represents similar atoms or groups to R^{105}], or salt thereof; or a solvate thereof.

[Claim 8] A sulfonyl derivative according to claim 7, wherein either one of R^{105} or $R^{105'}$ represents a halogen atom or an ethynyl group, or salt thereof; or a solvate thereof.

[Claim 9] A sulfonyl derivative according to any one of claims 1 to 8, wherein Q^3 represents the group:

[Chemical formula 16]



[wherein R^3, R^4, a, b and c have the same meanings as defined above], or salt thereof; or a solvate thereof.

[Claim 10] A sulfonyl derivative according to any one of claims 1 to 9, wherein T^1 represents a carbonyl group or a group $-CH(R^{13})-$ (wherein R^{13} has the same meaning as defined above), or salt thereof; or a solvate thereof.

[Claim 11] A medicament comprising as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 10.

[Claim 12] An inhibitor for an activated coagulation factor X, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 10.

[Claim 13] A coagulation suppressor comprising as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 10.

[Claim 14] A preventive and/or remedy for thrombosis or embolism, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 10.

[Claim 15] A preventive and/or remedy for cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of thrombus upon extracorporeal circulation or coagulation upon blood collection, which comprises as an effective ingredient a sulfonyl derivative or salt thereof, or a solvate thereof as claimed in any one of claims 1 to 10.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]

The present invention relates to a novel, orally-administrable sulfonyl derivative or salt thereof which inhibits an activated coagulation factor (which will hereinafter be abbreviated as "FXa"), thereby exhibiting strong anticoagulant action; and a coagulation suppressor or preventive and/or remedy for thrombosis or embolism which comprises the derivative or salt as an effective ingredient.

[0002]

[Prior Art]

Exasperation of coagulation capacity is an important factor for unstable angina, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization or formation of thrombus upon extracorporeal circulation. There is accordingly a demand for an excellent anticoagulant which is excellent in dose-responsiveness, has long-lasting effects, has a low risk of hemorrhage, has less side effects and exhibits rapid and sufficient effects even by oral administration (Thrombosis Research, **68**, 507-512, 1992).

[0003]

Studies on anticoagulants based on various acting mechanisms suggest that a FXa inhibitor has a possibility of becoming an excellent anticoagulant. The coagulation system

is a series of reactions wherein a large amount of a thrombus is produced through an amplification step due to a multi-stage enzymatic reaction and induces the formation of insoluble fibrin. In the intrinsic system, after the multi-stage reaction following the activation of a contact factor, activated Factor IX activates Factor X on a phospholipid membrane in the presence of activated Factor VIII and a calcium ion, while in the extrinsic system, activated Factor VII activates Factor X in the presence of a tissue factor. In other words, the activation of Factor X into FXa in the coagulation system is an essential reaction in the formation of thrombin. Activated Factor X (FXa) in each system carries out limited proteolysis of prothrombin, thereby forming thrombin. The resulting thrombin activates the coagulation factors on the upstream side, whereby the formation of thrombin is amplified further. As described above, the coagulation system upstream of FXa is separated into intrinsic and extrinsic systems so that the inhibition of the enzyme of the coagulation system upstream of FXa does not suppress the production of FXa sufficiently, inevitably resulting in the production of thrombin. Furthermore, the coagulation system conducts a self-amplifying reaction so that the suppression of the coagulation system can be accomplished more efficiently by the inhibition of FXa which exists upstream of the thrombin than by the inhibition of the thrombin formed (Thrombosis Research, **15**,

617-629(1979)).

[0004]

Another merit of the FXa inhibitor is that an effective dose in a thrombus model is largely different from the dose for extending the bleeding time in an experimental hemorrhage model. From the experimental result, the FXa inhibitor is presumed to be an anticoagulant with a low risk of hemorrhage.

[0005]

As a FXa inhibitor, various compounds are reported. In general, antithrombin III or antithrombin III-dependent penta-saccharide is known to have no inhibitory action against a prothrombinase complex which plays a practical role in the thrombus formation in vivo (Thrombosis Research, **68**, 507-512(1992); Journal of Clinical Investigation, **71**, 1383-1389(1983); Mebio, August issue, 92-97) and moreover, it does not exhibit effectiveness in oral administration. Although tick anticoagulant peptide (TAP) (Science, **248**, 593-596(1990)) or antistacin (AST) (Journal of Biological Chemistry, **263**, 10162-10167(1988)) isolated from a tick or leech which is a bloodsucker inhibits FXa and exhibits anti-thrombus effects on the models of from venous thrombus to arterial thrombus, it is not effective when orally administered because it is a high-molecular peptide. From such a viewpoint, a low-molecular FXa inhibitor which directly inhibits a coagulation factor with-

out depending on antithrombin III has been developed.

[0006]

[Problems Sought for Solution by the Invention]

An object of the present invention is to provide, as an excellent anticoagulant, a novel sulfonyl derivative or salt thereof, or a solvate thereof which has strong FXa inhibitory action, exhibits prompt, sufficient and long-lasting anti-thrombus effects even by the oral administration and has less side effects.

[0007]

[Means for the Solution of the Problems]

With the forgoing in view, the present inventors have carried out an extensive investigation on the synthesis of a novel FXa inhibitor and its pharmacological action. As a result, it has been found that a novel sulfonyl derivative or salt thereof, or solvate thereof exhibits strong FXa inhibitory action and strong anticoagulant action, inhibits FXa strongly, promptly and continuously by the oral administration, exhibits anti-coagulant action and anti-thrombus action, is highly safe and is useful as a preventive or remedy for various diseases caused by a thrombus·embolus.

[0008]

[Embodiments of the Invention]

The present invention relates to a sulfonyl derivative represented by the below-described formula (I) or salt thereof, or a solvate thereof.

[0009]

Chemical formula (I):

[0010]

[Chemical formula 17]

$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^3\text{-}SO_2\text{-}Q^A \qquad (I)$$

[wherein, Q^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent.

[0011]

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} alkynylene group,

a group $-N(R^1)-CO-$

(in which R^1 represents a hydrogen atom or an alkyl group),

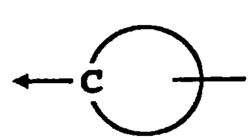
a group $-N(R^2)-(CH_2)_m-$

(in which R^2 represents a hydrogen atom or an alkyl group and m stands for an integer of 0 to 6), or

a group of the following formula:

[0012]

[Chemical formula 18]



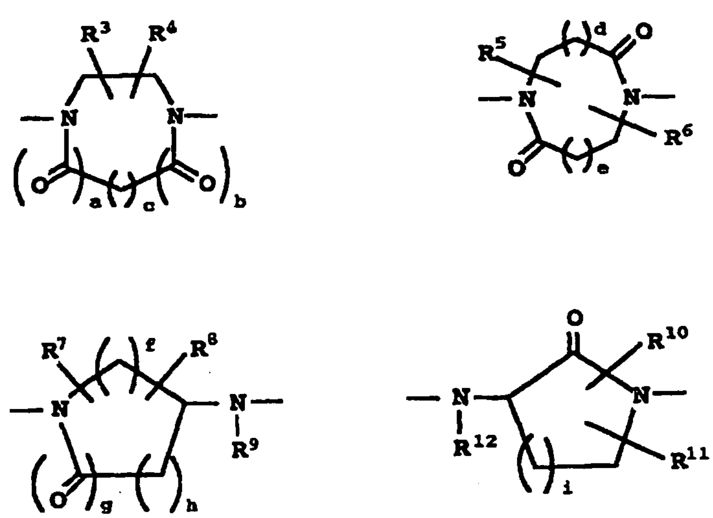
(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and ←C means the bonding of the carbon atom of this group to Q^1).

[0013]

Q^3 represents any one of the following groups.

[0014]

[Chemical formula 19]



(in which when the carbon atom to which each of R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} has been bonded is not adjacent to a nitrogen atom, R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} each independently represents a hydrogen atom,

a hydroxyl group,

an alkyl group,

an alkoxyl group,

an alkoxyalkyl group,

an alkoxyalkyloxy group,

a hydroxyalkyl group,

a hydroxyalkyloxy group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylsulfonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonylalkyl group,

a carboxyl group,

a carboxyalkyl group,

a carboxyalkyloxy group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkyloxy group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an amino group which may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents or

a group A^1-B^1- (in which A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^1 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group -NHCO or a group -NHCO-(C_{1-6} alkylene) group).

[0015]

When the carbon atom to which each of R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} has been bonded is adjacent to a nitrogen atom, R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} each independently represents

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylsulfonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonylalkyl group,

a carboxyl group,

a carboxyalkyl group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxyalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, or

a group A^2-B^2- (in which A^2 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, and B^2 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group -NHCO or a group -NHCO-(C_{1-6} alkylene) group).

[0016]

Each of R^3 and R^4, R^5 and R^6, R^7 and R^8, and R^{10} and R^{11} may be coupled together with a carbon atom which constitutes the ring and represent a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent, R^9 and R^{12}

each independently represents:

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

an alkoxyl group,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

a carboxyalkyl group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

an amino group which may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxycarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents or

an aminocarbonyloxyalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents.

[0017]

R^9 and R^7 or R^8 may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^9 has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0018]

R^{12} and R^{10} or R^{11} may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which R^{12}

has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0019]

a, b, d, e and g each independently stands for an integer of 0 or 1, c stands for an integer of 0 to 3, and f, h and i each independently represents an integer of 1 to 3, with the proviso that the sum of a, b and c stands for an integer of 2 or 3, the sum of d and e stands for an integer of 0 or 1 and the sum of f, g and h stands for an integer of 3 to 5)

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group Ar-C(H)=N- (in which, Ar represents an aryl group which may have a substituent), or a group Het-C(H)=N- (in which, Het represents a heteroaryl group which may have a substituent).

[0020]

T^1 represents a carbonyl group,

a group $-CH(R^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group having the hydroxyl group which may be protected, an alkoxyalkyl group, a carboxyalkyl group, an

alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, have a substituent (protecting group)) or

a group $-C(=NOR^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent.]. A sulfonyl derivative, or salt thereof; or solvate thereof.

A description will next be made of the substituents in the sulfonyl group derivative of the formula (I) according to the present invention.

<About group Q^A>

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group Ar-C(H)=N- (in which, Ar represents an aryl group which may have a substituent), or a group Het-C(H)=N- (in which, Het represents a heteroaryl group which may have a substituent).

[0021]

In the group Q^A, the term "arylalkenyl group which may

have a substituent" means a group composed of an aryl group and a linear, branched or cyclic C_{2-6} alkenylene group. Examples of the aryl group include phenyl, naphthyl, anthryl and phenanthryl group. Examples of the arylalkenyl group include phenylethenyl group.

[0022]

The "heteroarylalkenyl group which may have a substituent" means a group composed of a heteroaryl group and a linear, branched or cyclic C_{2-6} alkenylene group. The "heteroaryl group" means an aromatic monovalent group having at least one hetero atom and examples include pyridyl, furyl and thienyl groups. Examples of the heteroarylalkenyl group include pyridylethenyl group.

[0023]

The "saturated or unsaturated, dicyclic or tricyclic fused ring group which may have a substituent" means: 1) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered cyclic hydrocarbon groups which may have a substituent, 2) a group obtained by the condensation of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and 3) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered heterocyclic groups which may have a substituent.

[0024]

Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups. When the group has, similar to a cyclopentenyl group, plural structural isomers, they are all embraced in it.

[0025]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl, it is to be noted that they are all embraced in it.

[0026]

Examples of the group 1) include indenyl, indanyl, naphthyl, tetrahydronaphthyl, anthryl and phenanthryl; those of the group 2) include benzofuranyl, benzothienyl, indolyl, indolinyl, quinolyl, benzodiazinyl and tetrahy-

droisoquinolyl; and those of the group 3) include naphthyridinyl, tetrahydrothienopyridyl, tetrahydrothiazolopyridyl and tetrahydropyridinopyridyl.

[0027]

The aryl group in the group Ar-C(H)=N- (wherein Ar represents an aryl group which may have a substituent) means an aryl group similar to that described above. The group Ar-C(CH)=N- means a group composed of a phenyl group which may have a substituent and a group -C(H)=N- or the like.

[0028]

The heteroaryl group in the group Het-C(H)=N- (wherein Het represents a heteroaryl group which may have a substituent) means a heteroaryl group similar to that described above. The group Het-C(H)=N- means a group composed of a pyridyl group which may have a substituent and a group Het-C(H)=N-.

[0029]

Each of the arylalkenyl group, heteroarylalkenyl group, saturated or unsaturated dicylic fused ring group, saturated or unsaturated tricyclic fused ring group, the group Ar-C(H)=N- and the group Het-C(H)=N- may have 1 or 2 substituents. Examples of the substituent include a hydroxyl group, halogen atoms such as fluorine, chlorine, bromine and iodine, halogenomethyl groups having 1 to 3 halogen atoms substituted, an amino group, a cyano group,

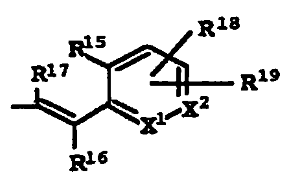
an aminomethyl group, an amidino group, a hydroxyamidino group, linear, branched or cyclic C_{1-6} alkyl groups (ex. methyl and ethyl), linear, branched or cyclic C_{1-6} alkoxyl groups (ex. methoxyl and ethoxyl), linear, branched or cyclic C_{2-7} alkoxycarbonylamidino groups (ex. methoxycarbonylamidino and ethoxycarbonylamidino), linear, branched or cyclic C_{2-6} alkenyl groups (ex. vinyl and allyl), linear, branched or cyclic C_{2-6} alkynyl groups (ex. ethynyl and propynyl), linear, branched or cyclic C_{2-6} alkoxycarbonyl groups (ex. methoxycarbonyl and ethoxycarbonyl) and aminocarbonyl groups.

[0030]

More specifically, the group Q^A represents any one of the following groups.

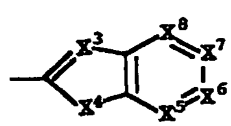
[0031]

[Chemical formula 20]



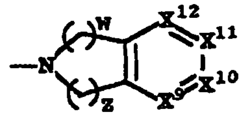
[0032]

[Chemical formula 21]



[0033]

[Chemical formula 22]



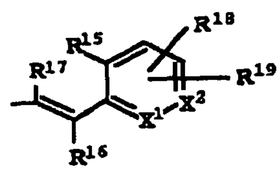
[0034]

A description will next be made of the substituent in these groups.

In the group

[0035]

[Chemical formula 23]



R^{15} represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, a halogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyl group, an alkoxyalkyl group, a carboxyl group, a carboxyalkyl group, an alkylcarbonyl group, an alkoxycarbonyl group, an alkoxycarbonyalkyl group, an alkylcarbonyloxy group or a group A^3-B^3 (wherein, A^3 represents an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylenecar-

bonyloxy group).

[0036]

In R^{15}, examples of the halogen atom include fluorine, chlorine, bromine and iodine.

[0037]

Examples of the alkyl group include linear, branched or cyclic C_{1-6} alkyl groups such as methyl, ethyl, isopropyl and cyclopropyl.

[0038]

The "hydroxyalkyl group" means a group composed of a hydroxyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples of the alkylene group include methylene, ethylene, trimethylene, propylene and cyclohexylene. Examples of the hydroxyalkyl group include hydroxymethyl and hydroxyethyl.

[0039]

The "alkoxyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkyl group and an oxygen atom. Examples include methoxyl, ethoxyl and isopropoxyl.

[0040]

The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkoxyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

[0041]

The "carboxyalkyl group" means a group formed of a

carboxyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include carboxymethyl and carboxyethyl.

[0042]

The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

[0043]

The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic alkoxyl group and a carbonyl group. Examples include methoxycarbonyl and ethoxycarbonyl.

[0044]

The "alkoxycarbonylalkyl group" means a group formed of a linear, branched or cyclic C_{2-7} alkoxycarbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include methoxycarbonylethyl and ethoxycarbonylmethyl.

[0045]

The "alkylcarbonyloxy group" means a group formed of a linear, branched or cyclic C_{2-7} alkylcarbonyl group and an oxygen atom. Examples include methylcarbonyloxy, ethylcarbonyloxy and isopropylcarbonyloxy.

[0046]

In the group A^3-B^3-, A^3 means an amino group which may have 1 or 2 substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a sub-

stituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent.

[0047]

When A^3 means an amino group which may have 1 or 2 substituents, B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylenecarbonyloxy group. The group A^3-B^3- therefore means, for example, a group as shown in the following class (A).

[0048]

Class (A):

an amino group which may have 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, may have 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, may have 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents and

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents.

[0049]

A description will next be made of the groups shown in Class (A).

[0050]

The "aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group which may have 1 or 2 substituents and a carbonyl group.

[0051]

The "aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group which may have 1 or 2 substituents and a linear, branched or cyclic C_{1-6} alkylene group. Examples of the aminoalkyl group include aminomethyl and aminoethyl.

[0052]

The "aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminocarbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples of the aminocarbonylalkyl group include aminocarbonylmethyl and aminocarbonylethyl.

[0053]

The "aminocarbonylalkyloxy group which may have, at the amino moiety, 1 or 2 substituents" means a group formed of the above-described aminocarbonylakyl group which may have a substituent and an oxygen atom. Examples of the aminocarbonylalkyloxy group include aminocarbonylmethoxyl

and aminocarbonylethoxyl.

[0054]

The "aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminoalkyl group which may have a substituent and a carbonyl group. Examples of the aminoalkylcarbonyl group include aminomethylcarbonyl and aminoethylcarbonyl.

[0055]

The "aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of the above-described aminoalkylcarbonyl group which may have a substituent and an oxygen atom. Examples of the aminoalkylcarbonyloxy group include aminomethylcarbonyloxy and aminoethylcarbonyloxy.

[0056]

Examples of the substituent which can be substituted for an amino group (moiety) include those as shown in the following Class (1).

[0057]

Class (1):

an alkyl group,

an alkenyl group,

a halogenoalkyl group,

a halogenoalkenyl group,

a hydroxyalkyl group,

a hyroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

an alkoxyl group,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

a formyl group,

a formylalkyl group,

a formylalkylcarbonyl group,

a formylalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

a carboxyalkyl group,

a carboxyalkylcarbonyl group,

a carboxyalkylsulfonyl group,

a carboxyalkylcarbonylalkyl group,

a carboxyalkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

a trifluoromethylsulfonyloxyalkenyl group and

a group a^3-b^3-

(wherein a^3 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group and an aminocarbonyl group.

b^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group, an alkylenecarbonyloxy group, an alkyleneaminocarbonyl group, an alkyleneaminocarbonylalkyl group, an alkyleneaminosulfonyl group or an alkyleneaminosulfonylalkyl group.

[0058]

The substituents which can be substituted for an amino group (moiety) in Class (1) will next be described.

[0059]

The "alkyl group" means a linear, branched or cyclic C_{1-6} alkyl group.

[0060]

The "alkenyl group" means a linear, branched or cyclic C_{2-6} alkenyl group. Examples include vinyl and allyl.

[0061]

The "halogenoalkyl group" means a group formed of a

halogen atom and a linear, branched or cyclic C_{1-6} alkylene group. Examples include chloromethyl and bromoethyl.

[0062]

The "halogenoalkenyl group" means a group formed of a halogen atom and a linear or branched C_{2-6} alkenylene group. Examples include chlorovinyl and bromoallyl groups. There is no particular limitation on the position of a double bond.

[0063]

The "hydroxyalkyl group" means a group formed of a hydroxyl group and a linear, branched or cyclic C_{2-6} alkylene group. Examples include hydroxyethyl and hydroxypropyl.

[0064]

The "hydroxyalkylcarbonyl group" means a group formed of the above-described hydroxyalkyl group and a carbonyl group. Examples include hydroxymethylcarbonyl and hydroxyethylcarbonyl.

[0065]

The "hydroxyalkylsulfonyl group" means a group formed of the above-described hydroxyalkyl group and a sulfonyl group. Examples include hydroxymethylsulfonyl and hydroxyethylsulfonyl.

[0066]

The "alkoxyl group" means a linear, branched or cyclic C_{1-6} alkoxyl group.

[0067]

The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkoxyl group and a linear, branched or cyclic C_{2-6} alkylene group. Examples include methoxyethyl, ethoxyethyl and methoxypropyl.

[0068]

The "alkoxyalkylcarbonyl group" means a group formed of the above-described alkoxyalkyl group and a carbonyl group. Examples include methoxyethylcarbonyl and ethoxymethylcarbonyl.

[0069]

The "alkoxyalkylsulfonyl group" means a group formed of the above-described alkoxyalkyl group and a sulfonyl group. Examples include methoxyethylsulfonyl and ethoxymethylsulfonyl.

[0070]

The "formylalkyl group" means a group formed of a formyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include formylmethyl and formylethyl.

[0071]

The "formylalkylcarbonyl group" means a group formed of the above-described formylalkyl group and a carbonyl group. Examples include formylmethylcarbonyl and formylethylcarbonyl.

[0072]

The "formylalkylsulfonyl group" means a group formed of the above-described formylalkyl group and a sulfonyl group. Examples include formylmethylsulfonyl and formylethylsulfonyl.

[0073]

The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

[0074]

The "alkylcarbonylalkyl group" means a group formed of the above-described alkylcarbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include methylcarbonylmethyl and ethylcarbonylmethyl.

[0075]

The "alkylsulfonyl group" means a group formed of the above-described alkyl group and a sulfonyl group. Examples include methylsulfonyl and ethylsulfonyl.

[0076]

The "alkylsulfonylalkyl group" means a group formed of the above-described alkylsulfonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include methylsulfonylmethyl and ethylsulfonylmethyl.

[0077]

The "carboxyalkyl group" means a group composed of a carboxyl group and a linear, branched or cyclic C_{1-6} alkylene group.

[0078]

The "carboxyalkylcarbonyl group" means a group formed of the above-described carboxyalkyl group and a carbonyl group. Examples include carboxymethylcarbonyl and carboxyethylcarbonyl.

[0079]

The "carboxyalkylsulfonyl group" means a group formed of the above-described carboxyalkyl group and a sulfonyl group. Examples include carboxymethylsulfonyl and carboxyethylsulfonyl.

[0080]

The "carboxyalkylcarbonylalkyl group" means a group formed of the above-described carboxyalkylcarbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include carboxymethylcarbonylmethyl and carboxyethylcarbonylmethyl.

[0081]

The "carboxyalkylsulfonylalkyl group" means a group formed of the above-described carboxyalkylsulfonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include carboxymethylsulfonylmethyl and carboxyethylsulfonylmethyl.

[0082]

The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkoxyl and a carbonyl group.

[0083]

The "alkoxycarbonylalkyl group" means a group formed of the above-described alkoxycarbonyl group and a linear, branched or cyclic C_{1-6} alkylene group.

[0084]

The "alkoxycarbonylalkylcarbonyl group" means a group formed of the above-described alkoxycarbonylalkyl group and a carbonyl group. Examples include methoxycarbonylethyl-carbonyl and ethoxycarbonylmethylcarbonyl.

[0085]

The "alkoxycarbonylalkylsulfonyl group" means a group of the above-described alkoxycarbonylalkyl group and a sul-fonyl group. Examples include methoxycarbonylethylsulfonyl and ethoxycarbonylmethylsulfonyl.

[0086]

The "trifluoromethylsulfonyloxyalkenyl group" means a group formed of a trifluoromethylsulfonyloxy group and a linear or branched C_{2-6} alkenylene group. Examples include trifluoromethylsulfonyloxyvinyl and trifluoromethylsulfony-loxyallyl.

[0087]

In the group a^3-b^3-, a^3 represents a saturated or un-saturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent such as a halogen atom. Examples of the saturated or unsaturated 5- or 6-membered

cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. Where the group has, as the cyclopentenyl, plural structural isomers, they are all embraced in it.

[0088]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl and triazinyl. Where the group has, as the pyranyl, plural structural isomers, they are all embraced in it.

[0089]

b^3 represents a single bond or a divalent group such as carbonyl, alkylene, carbonylalkyl, carbonylalkyloxy, alkylenecarbonyloxy, alkyleneaminocarbonyl, alkyleneaminocarbonylalkyl, alkyleneaminosulfonyl or alkyleneaminosulfonylalkyl. The "alkylene group" means a linear, branched or cyclic C_{1-6} alkylene group.

[0090]

The "carbonylalkyl group" means a group formed of a carbonyl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include carbonylmethyl and carbonylethyl.

[0091]

The "carbonylalkyloxy group" means a group formed of the above-described carbonylalkyl group and an oxygen atom. Examples include carbonylmethoxy and carbonylethoxy.

[0092]

The "alkylenecarbonyloxy group" means a group formed of a linear, branched or cyclic C_{1-6} alkylene group, a carbonyl group and an oxygen atom. Examples include methylenecarbonyloxy and ethylenecarbonyloxy.

[0093]

The "alkyleneaminocarbonyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkylene group, an imino group and a carbonyl group. Examples include methyleneaminocarbonyl and ethyleneaminocarbonyl.

[0094]

The "alkyleneaminocarbonylalkyl group" means a group formed of the above-described alkyleneaminocarbonyl and a linear, branched or cyclic C_{1-6} alkylene. Examples include methyleneaminocarbonylmethyl and ethyleneaminocarbonylmethyl.

[0095]

The "alkyleneaminosulfonyl group" means a group formed of a linear, branched or cyclic C_{1-6} alkylene group, an imino group and a sulfonyl group. Examples include methyleneaminosulfonyl and ethyleneaminosulfonyl.

[0096]

The "alkyleneaminosulfonylalkyl group" means a group formed of the above-described alkyleneaminosulfonyl and a linear, branched or cyclic C_{1-6} alkylene group. Examples include methyleneaminosulfonylmethyl and ethyleneaminosulfonylmethyl.

[0097]

A description will next be made of the substituents which can be introduced into a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or a saturated or unsaturated 5- or 6-membered heterocyclic group as the above-described a^3. Examples include halogen atoms, an alkoxyl group, an alkyl group, an alkoxycarbonyl and an aminocarbonyl group.

[0098]

As the group a^3-b^3-, there exist various kinds according to the combination of a^3 and b^3. Examples include:

a saturated or unsaturated, 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent

and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonylalkyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkylenecarbonyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkyleneaminocarbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkyleneaminocarbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkyleneaminosulfonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkyleneaminosulfonylalkyl group, and the like.

[0099]

In addition to the above-described Class (1), the following Class (2) can be given as examples of the substituent which can be substituted for the amino group (moiety).

[0100]

Class (2):

an amino group which may have 1 or 2 substituents selected from the above-described Class (1),

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminoalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected from the above-described Class (1),

an aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected the above-described from Class (1) and

an aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents selected the above-described from Class (1).

[0101]

A description will next be made of the substituents of Class (2).

[0102]

The aminoalkyl, aminocarbonyl, aminocarbonylalkyl and aminoalkylcarbonyl groups in Class (2) have the same meanings as described above.

[0103]

The "aminoalkyl group which may have a substituent at the amino moiety" means a group formed of the above-described amino group which may have a substituent and a

linear, branched or cyclic C_{2-6} alkylene group. Examples of the aminoalkyl group include aminoethyl and aminopropyl.

[0104]

The "aminocarbonylalkylcarbonyl group which may have a substituent at the amino moiety" means a group formed of the above-described aminocarbonylalkyl group which may have a substituent and a carbonyl group. Examples of the aminocarbonylalkylcarbonyl group include aminocarbonylmethylcarbonyl and aminocarbonylethylcarbonyl.

[0105]

The "aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminocarbonylalkyl group which may have a substituent and a sulfonyl group. Examples of the aminocarbonylalkylsulfonyl group include aminocarbonylmethylsulfonyl and aminocarbonylethylsulfonyl.

[0106]

The "aminosulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described amino group which may have a substituent and a sulfonyl group.

[0107]

The "aminosulfonylalkyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonyl group which may have a substituent and a linear, branched or cyclic C_{1-6} alkylene

group. Examples of the aminosulfonylalkyl group include aminosulfonylmethyl and aminosulfonylethyl.

[0108]

The "aminoalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminoalkyl group which may have the above-described substituent and a sulfonyl group. Examples of the aminoalkylsulfonyl group include aminomethylsulfonyl and aminoethylsulfonyl.

[0109]

The "aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonylalkyl group which may have a substituent and a carbonyl group. Examples of the aminosulfonylalkylcarbonyl group include aminosulfonylmethylcarbonyl and aminosulfonylethylcarbonyl.

[0110]

The "aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of the above-described aminosulfonylalkyl group which may have a substituent and a sulfonyl group. Examples of the aminosulfonylalkylsulfonyl group include aminosulfonylmethylsulfonyl and aminosulfonylethylsulfonyl.

[0111]

A^3 also represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group

which may have a substituent. Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups. Where the group has plural structural isomers as the cyclopentenyl group, they are all embraced in it.

[0112]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as pyranyl, they are all embraced in it.

[0113]

When A^3 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, B^3 represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylenecarbonyloxy group. Accordingly, the group A^3-B^3-, for example, represents a

group as shown in the following Class (B):

[0114]

Class (B):

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group

which may have a substituent, an alkylene group, a carbonyl group and an oxygen atom, and the like.

[0115]

A description will next be made of the groups shown in Class (B).

[0116]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group, examples of the group formed of the cyclic hydrocarbon group and a carbonyl group include cyclopentylcarbonyl and phenylcarbonyl; while those of the group formed of the heterocyclic group and a carbonyl group include furylcarbonyl, thienylcarbonyl and pyridylcarbonyl groups.

[0117]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and an alkylene group, the "group formed of a cyclic hydrocarbon group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group and a linear, branched or cyclic C_{1-6} alkylene group, for example, cyclohexylmethyl and benzyl, while the "group formed of a heterocyclic group and an alkylene group" means a group formed of the above-described heterocyclic group and a linear, branched or cyclic C_{1-6} alkylene group, for example, furylmethyl, thienylethyl and

pyridylpropyl.

[0118]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group and an alkylene group, the "group formed of a cyclic hydrocarbon group, a carbonyl group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group, a carbonyl group and a linear, branched or cyclic C_{1-6} alkylene group, for example, cyclopentadienylcarbonylmethyl and phenylcarbonylethyl, while the "group formed of a heterocyclic group, a carbonyl group and an alkylene group" means a group formed of the above-described heterocyclic group, a carbonyl group and a linear, branched or cyclic C_{1-6} alkylene group, for example, furylcarbonylmethyl, thienylcarbonylethyl and pyridylcarbonylpropyl.

[0119]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom, the "group formed of a cyclic hydrocarbon group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a cyclic hydrocarbon group, a carbonyl group and an alkylene group, and an oxygen atom, for example, cyclopentylcarbonylmethoxy and

phenylcarbonylethoxy, while the "group formed of a heterocyclic group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a heterocyclic group, a carbonyl group and an alkylene group, and an oxygen atom, for example, furylcarbonylmethoxy, thienylcarbonylethoxy and pyridylcarbonylpropoxy.

[0120]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group, "the group formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group and an alkylene group, and a carbonyl group, for example, cyclohexylmethylcarbonyl and phenylethylcarbonyl, while "the group formed of a heterocyclic group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a heterocyclic group and an alkylene group, and a carbonyl group, for example, furylmethylcarbonyl, thienylethylcarbonyl and pyridylpropylcarbonyl.

[0121]

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group, a

carbonyl group and an oxygen atom, "the group formed of a cyclic hydrocarbon group, an alkylene group, a carbonyl group and an oxygen atom" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group, and an oxygen atom, for example, cyclohexadienylmethylcarbonyloxy and phenylethylcarbonylyoxy, while "the group formed of a heterocyclic group, an alkylene group, a carbonyl group and an oxygen atom" means a group composed of the above-described group, which is formed of a heterocyclic group, an alkylene group and a carbonyl group, and an oxygen atom such as furylmethylcarbonyloxy, thienylethylcarbonyloxy and pyridylpropylcarbonyloxy.

[0122]

As examples of a substituent which can be substituted for the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group, those as shown below in Class (3) can be given. The number of the substituents which can be replaced is 1 to 3.

[0123]

Class (3):

a hydroxyl group,

an alkyl group,

an alkoxyl group,

a hydroxyalkyl group,

an alkoxyalkyl group,

a halogen atom,

a cyano group,

a nitro group,

a carboxyl group,

an alkoxycarbonyl group,

a formyl group,

a heteroaryl group,

a heteroarylalkyl group,

an alkylimino group,

an amidino group,

a guanidino group,

an amino(hydroxyimino)alkyl group,

an amino(alkoxyimino)alkyl group,

an amino(aryloxyimino)alkyl group,

an amino group which may have 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents, and

an oxygen atom.

[0124]

A description will next be made of the substituents which can be replaced for the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon or heterocyclic group in Class (3).

[0125]

The alkyl group, alkoxyl group, hydroxyalkyl group, alkoxyalkyl group, halogen atom, alkoxycarbonyl group, aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, and aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described above.

[0126]

The "heteroaryl group" means a monovalent aromatic group having at least one hetero atom. Examples include pyridyl, furyl and thienyl.

[0127]

The "heteroarylalkyl group" means a group formed of the above-described heteroaryl group and a linear, branched or cyclic C_{1-6} alkylene group. Examples include pyridylmethyl, furylethyl and thienylmethyl.

[0128]

The "alkylimino group" means a divalent group formed of a linear, branched or cyclic C_{1-6} alkyl group and a nitrogen atom. Examples include methylimino and ethylimino.

[0129]

The "amino(hydroxyimino)alkyl group" means a group having amino and hydroxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C_{1-6} alkyl group. Examples include amino(hydroxyimino)methyl and amino(hydroxyimino)ethyl.

[0130]

The "amino(alkoxyimino)alkyl group" means a group having amino and alkoxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C_{1-6} alkyl group. Here, the "alkoxyimino group" means a divalent group formed of the above-described alkoxyl group and an imino group. Examples of the amino(alkoxyimino)alkyl group include amino(methoxyimino)methyl and amino(ethoxyimino)methyl.

[0131]

The "amino(aryloxyimino)alkyl group" means a group having amino and aryloxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C_{1-6} alkyl group. Here, the "aryloxyimino group" means a divalent group formed of aryl and imino groups. Examples of the aryl group usable here include phenyl, naphthyl, anthryl and phenanthryl. Examples of the amino(aryloxyimino)alkyl group include amino(phenoxyimino)methyl and amino(naphthyloxyimino)methyl.

[0132]

The "aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents" means a group formed of an amino group having a substituent, a linear, branched or cyclic C_{2-6} alkylene group and an oxygen atom. Examples of the aminoalkyloxy group include aminoethyloxy and amino-propyloxy. Examples of the group which can be substituted for the amino moiety include those exemplified above.

[0133]

In the case of the cyclic hydrocarbon group, an oxygen atom can serve as a substituent when the corresponding keto compound is formed, while, in the case of the heterocyclic group or dicyclic or tricyclic fused ring group, an oxygen atom can serve as a substituent when the oxygen atom is bonded to a nitrogen or sulfur atom forming the ring and the corresponding N-oxide or S-oxide or keto compound is

formed.

[0134]

In the present invention, when R^{15} does not mean a C_{1-3} alkylene or alkenylene group together with R^{16} or R^{17}, preferred examples of R^{15} include a hydrogen atom, an alkyl group, a hydroxyalkyl group and a group A^3-B^3-.

[0135]

In R^{16} and R^{17}, examples of the halogen atom include fluorine, chlorine, bromine and iodine.

[0136]

The "alkyl group" means a linear, branched or cyclic C_{1-8} alkyl group. Examples include methyl, ethyl, isopropyl, cyclopropyl, heptyl and octyl.

[0137]

The "hydroxyalkyl group" means a group formed of a hydroxyl group and a linear, branched or cyclic C_{1-8} alkylene group. Examples include hydroxymethyl and hydroxyethyl.

[0138]

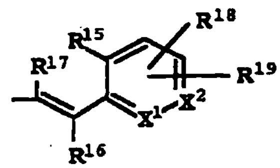
The "alkoxyalkyl group" means a group formed of the above-described alkyl group, an oxygen atom and a linear, branched or cyclic C_{1-8} alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

[0139]

When R^{16} or R^{17} forms a C_{1-3} alkylene or alkenylene group together with R^{15}, the following group:

[0140]

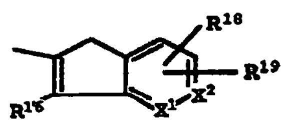
[Chemical formula 24]



means the following group:

[0141]

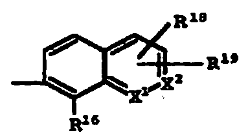
[Chemical formula 25]



[0142]

[Chemical formula 26]

or



[0143]

In the present invention, when R^{16} or R^{17} does not mean a C_{1-3} alkylene or alkenylene group together with R^{15}, a hydrogen atom and alkyl group are preferred as R^{16} or R^{17}.

[0144]

In the present invention, it is preferred that R^{15} and R^{16} or R^{17} are coupled together to form a C_{1-3} alkylene or alkenylene group.

[0145]

R^{18} and R^{19} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted with an alkylsilyl group as a protecting group, a trifluoromethyl group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group (with the proviso that R^{18} and R^{19} do not represent a hydrogen atom at the same time).

[0146]

In R^{18} and R^{19}, the halogen atom, halogenoalkyl group, alkyl group, alkoxyl group, alkenyl group and aminoalkyl group mean have the same meaning as described above.

[0147]

The "alkylaminoalkyl group" means a group wherein the amino group of the aminoalkyl moiety have been substituted with 1 or 2 linear, branched or cyclic alkyl groups and examples include methylaminomethyl and ethylmethylaminomethyl.

[0148]

The "alkynyl group which may be substituted with an alkylsilyl group as a protecting group" means an alkynyl group which may be substituted with an alkylsilyl group such as trimethylsilyl, triethylsilyl, tertiary butyldimethylsilyl or dimethylphenylsilyl group as a protecting

group.

[0149]

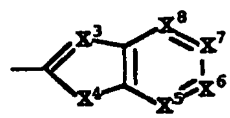
In the present invention, as R^{18} or R^{19}, a halogen atom and alkynyl group are preferred, with a chlorine atom, bromine atom and ethynyl group are particularly preferred.

[0150]

X^3 in the group:

[0151]

[Chemical formula 27]



means a nitrogen atom or a group $=C(R^{100})-$ (wherein, R^{100} represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxycarbonyl group, an aralkyloxycarbonylalkyl group, an alkoxycarbonylalkyl group, a nitro group, an amino group which may have a protecting group or an aminoalkyl group which may have, at the amino moiety thereof, a protecting group).

[0152]

The halogen atom, alkyl group, alkoxycarbonyl group, aryloxycarbonylalkyl group, alkoxycarbonylalkyl group, aryloxycarbonylalkyl group in R^{100} have the same meanings as described above, respectively. The amino group which may have a protecting group or aminoalkyl group which may have, at the amino moiety thereof, a protecting group mean amino

and aminoalkyl groups which may have an ordinarily known protecting group, respectively.

[0153]

X^4 represents an oxygen atom, a sulfur atom or a group $-N(R^{101})-$

(wherein R^{101} means a hydrogen atom, an alkyl group, an alkoxycarbonyl group, an aralkyloxycarbonyl group, an alkoxycarbonylalkyl group, an alkylsulfonyl group or an arylsulfonyl group).

[0154]

The alkyl group, alkoxycarbonyl group, aralkyloxycarbonyl group, alkoxycarbonylalkyl group, alkylsulfonyl group and arylsulfonyl group in R^{101} have the same meanings as described above, respectively.

[0155]

X^5 and X^8 each independently represents a nitrogen atom or a group $-C(R^{102})$

(wherein, R^{102} represents a hydrogen atom or a halogen atom) and the halogen atom in R^{102} has the same meaning as described above.

[0156]

X^6 and X^7 each independently represents a nitrogen atom or

a group $-C(R^{103})-$

(wherein R^{103} represents a hydrogen atom, a hydroxyl group,

a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group.

[0157]

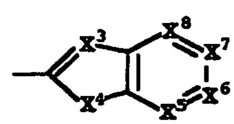
The halogen atom, halogenoalkyl group, alkyl group, alkoxyl group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group, alkoxycarbonylamidino group in R^{103} have the same meanings as described above.

[0158]

It is preferred that the group:

[0159]

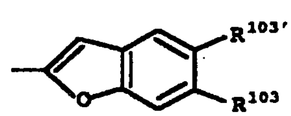
[Chemical formula 28]



means any one of the following groups:

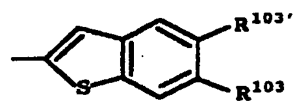
[0160]

[Chemical formula 29]



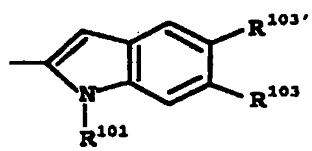
[0161]

[Chemical formula 30]



[0162]

[Chemical formula 31]



[wherein R^{101} and R^{103} have the same meanings as described above and $R^{103'}$ means those similar to R^{103}].

[0163]

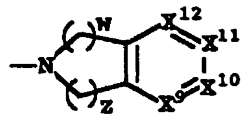
As R^{101}, a hydrogen atom is particularly preferred. It is preferred that either one of R^{103} and $R^{103'}$ represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the halogen atom, ethynyl group, amidino group, hydroxyamidino group and methoxycarbonylamidino group being particularly preferred.

[0164]

In the group:

[0165]

[Chemical formula 32]



X^9 and X^{12} each independently represents a nitrogen atom or a group $-C(R^{104})-$ (wherein R^{104} represents a hydrogen atom or a halogen atom) and the halogen atom as R^{104} is similar to that described above.

[0166]

X^{10} and X^{11} each independently represents a nitrogen atom or a group $-C(R^{105})-$ (wherein R^{105} represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group.

[0167]

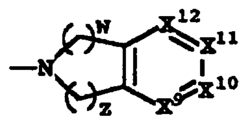
The halogen atom, halogenoalkyl group, alkyl group, alkoxyl group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group and alkoxycarbonylamidino group in R^{105} have the same meanings as described above.

[0168]

The group:

[0169]

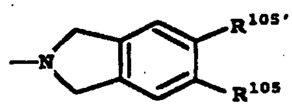
[Chemical formula 33]



preferably represents the following group:

[0170]

[Chemical formula 34]



[wherein R^{105} has the same meanings as described above and $R^{105'}$ is similar to that described as R^{105}].

[0171]

It is preferred that either one of R^{105} and $R^{105'}$ represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the halogen atom, ethynyl group, amidino group, hydroxyamidino group and methoxycarbonylamidino group being particularly preferred.

[0172]

<About the group Q^1>

Q^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered

heterocyclic group which may have a substituent.

[0173]

Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has plural structural isomers as cyclopentenyl, they are all embraced in it.

[0174]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, pyrazinyl, tetrahydropyrazinyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, thiazolidinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyrimidinyl, tetrahydropyrimidinyl, pyridazinyl, tetrahydropyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as pyranyl, they are all embraced in it.

[0175]

Examples of the substituent which can be replaced for the above-described saturated or unsaturated 5- or 6-

membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group include the groups shown in the below-described Class (4). The number of the replaceable substituents ranges from 1 to 4.

[0176]

Class (4):

a hydroxyl group,

an alkyl group,

an alkenyl group,

a halogenoalkyl group,

a halogenoalkenyl group,

an alkoxyl group,

a hydroxyalkyl group,

an alkoxyalkyl group,

a halogen atom,

a cyano group,

a nitro group,

a carboxyl group,

an alkoxycarbonyl group,

a formyl group,

a heteroaryl group,

a heteroarylalkyl group,

an alkylimino group,

an alkylsulfonyl group,

an amidino group,

a guanidino group,

an amino(hydroxyimino)alkyl group,

an amino(alkoxyimino)alkyl group,

an amino(aryloxyimino)alkyl group,

an amino group which may have 1 or 2 substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, 1 or 2 substituents,

an oxygen atom,

a trifluoromethyl group,

a trifluoromethylsulfonyloxy group,

a trifluoromethylsulfonyloxyalkenyl group,

a boric acid group ($-B(OH_2)$),

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have 1 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl, alkyl, cyano, nitro, carboxyl, alkoxycarbonyl, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminosulfonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents and trifluoromethyl, and

a saturated or unsaturated 5- or 6-membered heterocyclic group which may have 1 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl, alkyl, cyano, nitro, carboxyl, alkoxycarbonyl, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminosulfonyl which may have, at the amino-moiety thereof, 1 or 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents and trifluoromethyl.

[0177]

The substituents in Class (4) have the same meanings as described in Classes (1) to (3) of the description of the group Q^A.

[0178]

In the present invention, preferred examples of Q^1 include a cyclopentyl group which may have a substituent, cy-

clohexyl group which may have a substituent, cyclopentenyl group which may have a substituent, cyclohexenyl group which may have a substituent, phenyl group which may have a substituent, pyrrolidinyl group which may have a substituent, piperidinyl group which may have a substituent, imidazolyl group which may have a substituent, thiazolyl group which may have a substituent, thiadiazolyl group which may have a substituent, pyridyl group which may have a substituent, pyrimidinyl group which may have a substituent, pyridazinyl group which may have a substituent, thiazolydinyl group which may have a substituent, morpholinyl group which may have a substituent, piperazinyl group which may have a substituent, thiomorpholinyl group which may have a substituent, pyrrolyl group which may have a substituent, thienyl group which may have a substituent, furanyl group which may have a substituent, tetrahydropyrimidinyl group which may have a substituent, tetrahydrofuranyl group which may have a substituent, tetrahydrothienyl group which may have a substituent, sulforanyl group which may have a substituent, imidazolinyl group which may have a substituent, thiazolinyl group which may have a substituent, oxazolyl group which may have a substituent, oxadiazinyl group which may have a substituent, triazinyl group which may have a substituent, tetrazinyl group which may have a substituent, pyrazinyl group which may have a substituent, pyrazolyl group which may have a substituent, pyrazolinyl group which

may have a substituent and pyrazolidinyl group which may have a substituent.

[0179]

Preferred examples of the substituent include a hydroxyl group, an alkyl group, a hydroxyalkyl group, a halogen atom, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group, a formyl group, an alkylsulfonyl group, an amino group which may have 1 or 2 substituents, an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an oxygen atom, a trifluoromethyl group, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents and a trifluoromethyl group, and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano

group, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an aminosulfonyl group which may have, at the amino moiety thereof, 1 or 2 substituents, an aminoalkyl group which may have, at the amino moiety thereof, 1 or 2 substituents and a trifluoromethyl group.

[0180]

<About the group Q^2>

The group Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, a linear or branched C_{2-6} alkenylene group, a linear or branched C_{2-6} alkynylene group,

a group $-N(R^1)-CO-$

(wherein, R^1 represents a hydrogen atom or an alkyl group),

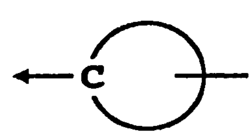
a group $-N(R^2)-(CH_2)m-$

(wherein R^2 represents a hydrogen atom or an alkyl group and m stands for an integer of 0 to 6), or

a group:

[0181]

[Chemical formula 35]



(which represents a divalent, saturated or unsaturated 5-

or 6-membered cyclic hydrocarbon group which may have a substituent,

a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or

a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and ←C means the bonding of the carbon atom of this group to Q^1),

[0182]

In Q^2, examples of the linear or branched C_{1-6} alkylene group include methylene, ethylene, trimethylene, propylene, tetramethylene, butylene, pentamethylene and hexamethylene.

[0183]

Examples of the linear or branched C_{2-6} alkenylene group include vinylene, propenylene, butenylene and pentenylene. There is no particular limitation on the position of the double bond.

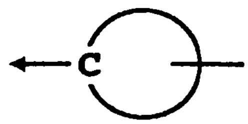
[0184]

Examples of the linear or branched C_{2-6} alkynylene group include propynylene, butynylene, pentynylene and hexynylene.

The group of the following formula:

[0185]

[Chemical formula 36]



means a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a divalent saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or a divalent saturated or unsaturated dicyclic fused ring group which may have a substituent and $\leftarrow\dot{C}$ means the bonding of the carbon atom of this group to Q^1. Examples of the group include divalent groups derived from thiophene, furan,. pyran, pyrrole, pyrrolidine, pyrroline, imidazole, imidazoline, imidazolidine, pyrazole, pyrazolidine, thiazole, oxazole, oxathiolane, benzene, pyridine, piperidine, piperazine, morpholine, thiomorpholine, pyrazine, pyrimidine, pyridazine, triazine, tetrazine, thiadiazine, dithiazine, cyclopentane, cyclopetene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, or the like and they may have a substituent. Examples of the substituent are similar to those exemplified in Class (4).

[0186]

The alkyl group in R^1 or R^2 of the group $-N(R^1)-CO-$ or $-N(R^2)-(CH_2)_m-$ means a linear, branched or cyclic C_{1-6} alkyl group. Examples include methyl, ethyl, isopropyl and cyclopropyl. As the group $-N(R^1)-CO-$, a group $\leftarrow N(R^1)-CO-$

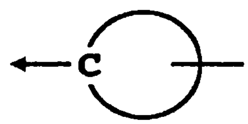
(wherein ← means the bonding of the nitrogen atom of this group to Q^1) is preferred, while as the group $-N(R^2)-(CH_2)_m-$, a group $\leftarrow N(R^2)-(CH_2)_m-$ (wherein ← means the bonding of the nitrogen atom of this group to Q^1) is preferred.

[0187]

In the present invention, Q^2 preferably represents a single bond, a carbonyl group or a group

[0188]

[Chemical formula 37]

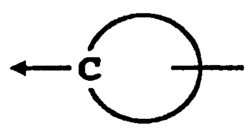


.

Among the groups represented by the group:

[0189]

[Chemical formula 38]



,

divalent groups derived from benzene, pyrimidine, tetrahydropyrimidine, pyrazine, pyridazine, triazine, tetrazine, imidazole, imidazoline, thiazole, thiazoline, furan, thiophene, pyrrole, oxazole, oxazoline, thiadiazole, cyclopentane, cyclopentene, cyclohexane or cyclohexene.

[0190]

<About the group Q^3>

In R^3, R^4, R^5, R^6, R^7, R^8, R^{10} and R^{11} as the substituents in Q^3, the alkyl, alkoxyl, alkoxyalkyl, hydroxyalkyl, hydroxyalkyloxy, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylalkylsulfonyl, amino which may have 1 to 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxy which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkylcarbonyloxy which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, and aminocarbonylalkyloxy which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described above in R^{15} of the description of the group Q^A.

[0191]

The "alkoxyalkyloxy group" means a group formed of the above-described alkoxyalkyl group and an oxygen atom and examples include methoxymethyloxy, methoxyethyloxy and

ethoxymethyloxy.

[0192]

The "carboxyalkyloxy group" means a group formed of the above-described carboxyalkyl group and an oxygen atom and examples include carboxymethoxyl and carboxyethoxyl.

[0193]

The "alkoxycarbonylalkyloxy group" means a group formed of the above-described alkoxycarbonylalkyl group and an oxygen atom and examples include methoxycarbonylethyl and ethoxycarbonylethyl.

[0194]

In the group A^1-B^1-, A^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, various structural isomers they are all embraced in it.

[0195]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or

6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl group, they are all embraced in it.

[0196]

B^1 represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group -NHCO- or a group -NHCO-(C_{1-6} alkylene).

[0197]

Examples of the group A^1-B^1- include the following groups:

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonyl group, and

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group.

[0198]

Each of R^3 and R^4, R^5 and R^6, R^7 and R^8, and R^{10} and R^{11}

are coupled together with a carbon atom which constitutes the ring and represents a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 7-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, various structural isomers, they are all embraced in it.

[0199]

The saturated or unsaturated 5- to 7-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0200]

In R^9 or R^{12} as the substituent in Q^3, the alkyl, hydroxyalkyl, alkoxyl, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxyalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylalkylsulfonyl, amino which may have 1 to 2 substituents, aminoalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxy which may have, at the amino moiety thereof, 1 to 2 substituents, aminoalkylcarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminoalkyloxycarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonyl which may have, at the amino moiety thereof, 1 or 2 substituents, aminocarbonylalkyl which may have, at the amino moiety thereof, 1 or 2 substituents, and aminocarbonyloxyalkyl which may have, at the amino moiety thereof, 1 or 2 substituents have the same meanings as described in Q^A.

[0201]

In the group A^2-B^2-, A^2 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or

6-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has, similar to a cyclopentenyl group, plural structural isomers, they are all embraced in it.

[0202]

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0203]

B^2 represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group -NHCO- or a group -NHCO-(C_{1-6} alkylene).

[0204]

Examples of the group A^2-B^2- include the following groups:

a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonyl group, and

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkylene group.

[0205]

R^9 and R^7, R^9 and R^8, R^{12} and R^{10}, and R^{12} and R^{11} are each coupled together with the carbon atom which constitutes the ring and the nitrogen atom to which R^9 or R^{12} has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, the saturated or unsaturated 5- to 7-membered heterocyclic group is a cyclic group which has at least one nitrogen atom and may have a hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl,

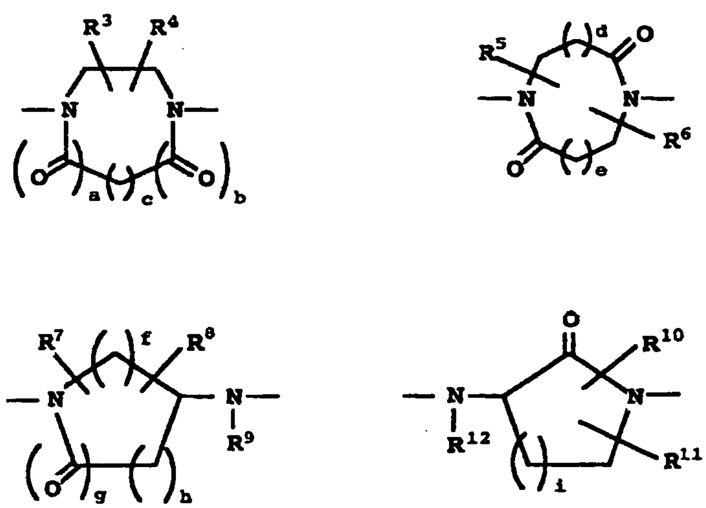
piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, triazolyl and triazinyl. Where the group has, similar to a pyranyl group, plural structural isomers, they are all embraced in it.

[0206]

In the present invention, Q^3 represents a group of the following formula:

[0207]

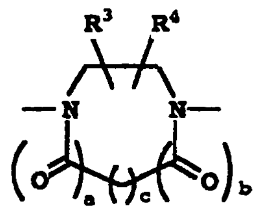
[Chemical formula 39]



(wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, a, b, c, d, e, f, g, h and i have the same meanings as described above). Preferred as Q^3 is a group of the following formula:

[0208]

[Chemical formula 40]



(wherein R^3, R^4, a, b and c have the same meanings as described above), of which the group wherein:

R^3 and R^4 each independently represents

a hydrogen atom,

a carboxyl group,

a carboxyalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

a carboxyalkylaminocarbonyl group,

a carboxyalkylaminocarbonylalkyl group,

an alkoxycarbonylalkylaminocarbonyl group,

an alkoxycarbonylalkylaminocarbonylamino group,

a carbamoyl group,

a monoalkylcarbamoyl group,

a dialkylcarbamoyl group,

a carbamoylalkyl group,

a monoalkylcarbamoylalkyl group,

a dialkylcarbamoylalkyl group,

a morpholinylcarbonyl group

a morpholinylcarbonylalkyl group,

a tetrazolylaminocarbonyl group,

a tetrazolylaminocarbonylalkyl group,

a tetrazolylalkyl group,

a tetrazolylalkylaminocarbonyl group, or

a tetrazolylalkylaminocarbonylamino group,

a stands for 0, b stands for 0 and c stands for 2 is more preferred.

[0209]

<About the group T^1>

T^1 represents a carbonyl group,

a group $-CH(R^{13})-$

(in which R^{13} represents a hydrogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent) or

a group $-C(=NOR^{14})-$

(in which R^{14} represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxycarbonyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent).

[0210]

Here, in R^{13} and R^{14}, the alkyl, carboxyalkyl, alkoxycarbonyl, aryl, aralkyl, heteroaryl, heteroarylalkyl and

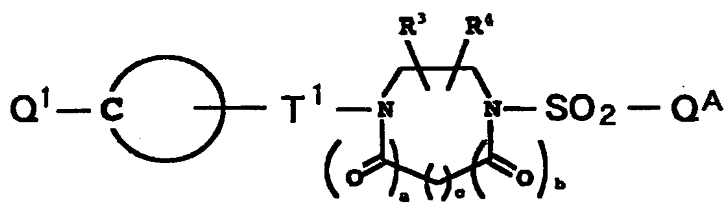
aminoalkyl which may have, at the amino moiety thereof, a substituent have the same meanings as described in Q^A. In the present invention, a carbonyl group is preferred as T^1.

[0211]

In the present invention, compounds represented by the below-described formula are preferred.

[0212]

[Chemical formula 41]



[wherein, Q^1, Q^A, T^1, R^3, R^4, a, b and c have the same meanings as described above].

The sulfonyl derivative of the present invention has optical isomers or stereoisomers based on an asymmetric carbon atom. These optical isomers and stereoisomers and mixtures thereof are all embraced in the present invention.

[0213]

Although there is no particular limitation imposed on the salt of the sulfonyl derivative according to the present invention insofar as it is a pharmaceutically acceptable salt. Specific examples include salts of a mineral acid such as hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate and sulfate, salts of an organic sulfonic acid such as benzoate, methanesulfonate, 2'-hydroxyethanesulfonate and p-

toluenesulfonate and salts of an organic carboxylic acid such as acetate, propanoate, oxalate, malonate, succinate, glutarate, adipate, tartrate, maleate, malate and mandelate. There is no particular limitation imposed on the solvate insofar as it is pharmaceutically acceptable. Specific examples include hydrates and ethanolates.

[0214]

The following are the preferred compounds as the sulfonyl derivative of the present invention.

[0215]

In the present invention, in addition to the above-exemplified compounds, salts thereof and solvates thereof can be mentioned as preferred examples.

[0216]

The process for the preparation of the sulfonyl derivative of the present invention will next be described.

[0217]

The sulfonyl derivative or salt thereof, or solvate thereof according to the present invention can be prepared by using general, conventionally-known chemical processes in combination. Typical synthesis processes will be described subsequently.

[0218]

Upon synthesis of the sulfonyl derivative of the present invention, when it is necessary to protect a substituent such as nitrogen atom, hydroxyl group or carboxyl group, it may be

protected with an ordinary, conventionally-known protecting group which can be removed as needed. Such a protecting group can be removed at need by the synthesis process ordinarily employed in the organic chemistry which will be described below.

[0219]

The starting materials necessary for the synthesis can be obtained by the synthesis process ordinarily employed in the organic chemistry and such a process will be described in Referential Examples. The starting materials for the sulfonyl derivative of the present invention can also be synthesized by the application of the process described in Referential Examples.

[0220]

A description will next be made of a protecting group for the substituent such as nitrogen atom, hydroxyl group or carboxyl group and deprotection process thereof.

[0221]

As a protecting group for the nitrogen atom in an amino or alkylamino group, ordinary acyl-type protecting groups are suited. Examples include alkanoyl groups such as acetyl, alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and tertiary butoxy carbonyl, arylmethoxycarbonyl groups such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl and para-(ortho-)nitrobenzyloxycarbonyl groups, arylmethyl groups such as benzyl and triphenylmethyl and aroyl groups such as benzoyl. The removing process of such a protecting group differs with

the chemical properties of the protecting group adopted. For example, the acyl-type protecting group such as alkanoyl, alkoxycarbonyl or aroyl can be removed by hydrolysis using an appropriate base such as alkali metal hydroxide, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

[0222]

The substituted methoxycarbonyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by using an appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. The arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para-(ortho-)nitrobenzyloxycarbonyl, or the arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. The benzyl group can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium, whereby conversion into a nitrogen-hydrogen bond can be effected. The triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst.

[0223]

In addition to the above-described amino-protecting group, a phthaloyl type protecting group can be adopted for a primary amino group and it can be removed using hydrazine, dimethylaminopropylamine or the like.

[0224]

As the protecting group suited for a hydroxyl group, there are acyl type and ether type ones. Examples of the acyl type protecting group include alkanoyl groups such as acetyl and aroyl groups such as benzoyl, while those of the ether type protecting group include arylmethyl groups such as benzyl, silyl ether groups such as tertiary butyl dimethylsilyl, methoxymethyl and tetrahydropyranyl. The removal of such a protecting group differs with the chemical properties of the protecting group adopted. For example, the acyl group such as alkanoyl or aroyl can be removed by the hydrolysis using an appropriate base such as an alkali metal hydroxide, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide. The arylmethyl type protecting group can be removed by the hydrogenolysis using a palladium-carbon catalyst. The silyl group such as tertiary butyl dimethylsilyl can be removed using a hydrofluoride such as tetrabutyl ammonium fluoride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid, hydrochloric acid or the like. The hydroxyl group substituted for an aryl group can be protected with a methyl group and deprotection can be carried out using a Lewis acid

such as aluminum chloride, boron trifluoride or phosphorus tribromide, trimethylsilyl iodide or hydrogen bromide.

[0225]

A carboxyl group can be protected by the esterification of it. A methyl or ethyl ester can be deprotected by the hydrolysis using an appropriate base such as alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide, while from a tertiary butyl ester, the tertiary butyl group can be removed by treating with trifluoroacetic acid or hydrochloric acid. From an arylmethyl type ester such as benzyl, the arylmethyl group can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst.

[0226]

[Preparation process-1]

A process for preparing a sulfonyl derivative represented by the following formula (I):

[0227]

[Chemical formula 43]

$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^3\text{-}SO_2\text{-}Q^4 \qquad \text{(I)}$$

[wherein Q^1, Q^2, Q^3, Q^4 and T^1 have the same meanings as described above], which comprises sulfonylating the nitrogen atom of Q^{3a} of the compound represented by the following formula (Ia):

[0228]

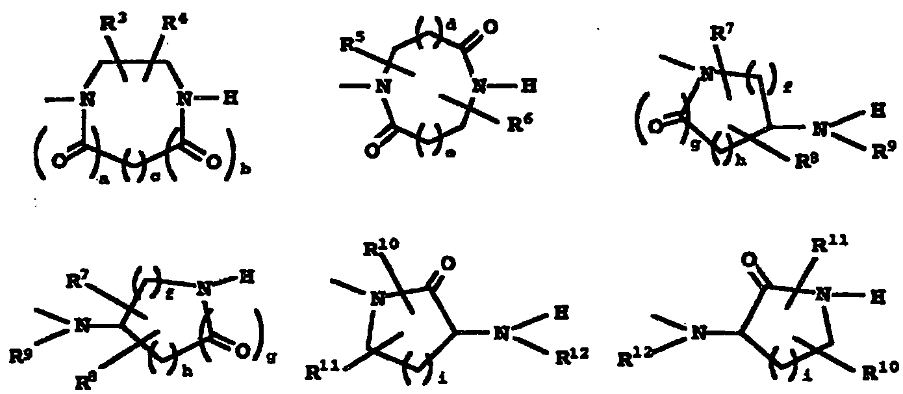
$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^{3a} \qquad \text{(Ia)}$$

[wherein Q^1, Q^2 and T^1 have the same meanings as described above

and Q^{3a} represents any one of the groups represented by the following formulas:

[0229]

[Chemical formula 42]



(in which R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, a, b, c, d, e, f, g, h and i have the same meanings as described above)] with a sulfonic acid halide represented by the following formula (IIa):

[0230]

$$\text{Halo-}SO_2\text{-}Q^4 \qquad \text{(IIa)}$$

[wherein Q^4 has the same meaning as described above and Halo represents a halogen atom such as chlorine, bromine or iodine].

[0231]

<Synthesis of the compound of the formula (Ia)>

The compound of the formula (Ia) can be synthesized by a series of procedures in accordance with the known technique.

[0232]

For example, a compound of the following formula (Ib):

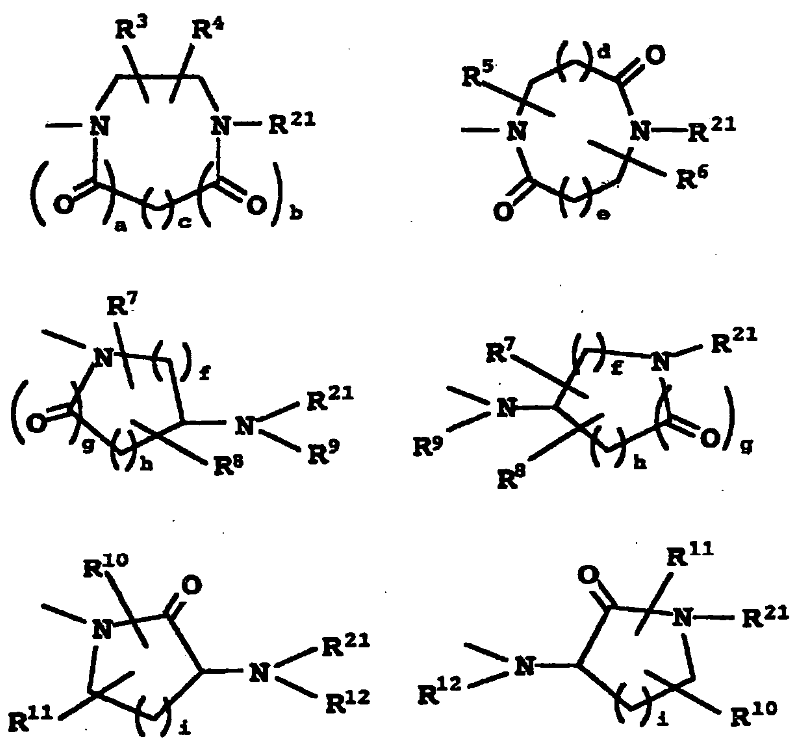
[0233]

$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^{3b} \qquad \text{(Ib)}$$

[wherein Q^1, Q^2 and T^1 have the same meanings as described above and Q^{3b} represents any one of the following groups:

[0234]

[Chemical formula 44]



(wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, a, b, c, d, e, f, g, h and i have the same meanings as described above and R^{21} represents an ordinary nitrogen protecting group such as tertiary butoxycarbonyl, benzyloxycarbonyl, paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl)] can be synthesized by acylating the nitrogen atom of the compound – which can be synthesized in a conventionally known

manner or by application thereof and is represented by the following formula (IIIa):

$$Q^{3b}\text{-}H \qquad \text{(IIIa)}$$

(wherein Q^{3b} has the same meaning as described above) - to which the hydrogen atom of Q^{3b} has been bonded, with a carboxylic acid in an activated form represented by any one of the following formulas (Iva) to (Ivd):

[0235]

$$Q^1\text{-}Q^{2b}\text{-}COOH \qquad \text{(IVa)}$$

[0236]

$$Q^1\text{-}N(R^{20})\text{-}(CH_2)_{m1}\text{-}COOH \qquad \text{(IVb)}$$

[0237]

$$Q^1\text{-}O\text{-}(CH_2)_{m1}\text{-}COOH \qquad \text{(IVc)}$$

[0238]

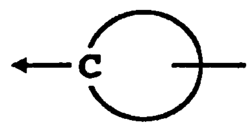
$$Q^1\text{-}S\text{-}(CH_2)_{m1}\text{-}COOH \qquad \text{(IVd)}$$

[0239]

[wherein Q^1 has the same meaning as described above, R^{20} represents an ordinary nitrogen protecting group such as linear or branched alkylkylene, tertiary butoxycarbonyl, benzyloxycarbonyl, paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl, Q^{2b} represents a single bond, a linear or branched C_{1-6} alkylene, a linear or branched C_{2-6} alkenylene, a linear or branched C_{2-6} alkynylene or a group of the following formula:

[0240]

[Chemical formula 45]



(which has the same meaning as described above) and m1 stands for an integer of 1 to 6].

[0241]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) forms an amide bond, the compound of the formula (Ib) can be synthesized by alkylating the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) with any one of the compounds represented by the following formulas (Va) to (Vd):

[0242]

Q^1-Q^{2b}-CHL^1R^{13} (Va)

[0243]

Q^1-$N(R^{20})$-$(CH_2)_{m1}$-CHL^1R^{13} (Vb)

[0244]

Q^1-O-$(CH_2)_{m1}$-CHL^1R^{13} (Vc)

[0245]

Q^1-S-$(CH_2)_{m1}$-CHL^1R^{13} (Vd)

[0246]

[wherein Q^1, Q^{2b}, R^{13}, R^{20} and m1 have the same meanings as described above, and L^1 represents an eliminating group frequently used in the organic chemistry, such as chlorine, bromine, iodine, methylsulfonyloxy or

paratoluenesulfonyloxy].

[0247]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be prepared by reductive alkylation, that is, by forming the corresponding imine with a carbonyl compound represented by any one of the following formulas (VIa) to (VId):

[0248]

Q^1-Q^{2b}-C(=O)R^{13} (VIa)

[0249]

Q^1-N(R^{20})-$(CH_2)_{m1}$-C(=O)R^{13} (VIb)

[0250]

Q^1-O-$(CH_2)_{m1}$-C(=O)R^{13} (VIc)

[0251]

Q^1-S-$(CH_2)_{m1}$-C(=O)R^{13} (VId)

[0252]

[wherein Q^1, Q^{2b}, R^{13}, R^{20} and m1 have the same meanings as described above], followed by reduction; by reacting the compound of the formula (IIIa) with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole and a compound containing a primary amine represented by any one of the following formulas (VIIa) to (VIId):

[0253]

Q^1-Q^{2b}-NH_2 (VIIa)

[0254]

Q^1-N(R^{20})-$(CH_2)_{m2}$-NH_2 (VIIb)

[0255]

Q^1-O-$(CH_2)_{m2}$-NH_2 (VIIc)

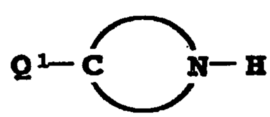
[0256]

Q^1-S-$(CH_2)_{m2}$-NH_2 (VIId)

[0257]

[0258]

[Chemical formula 46]

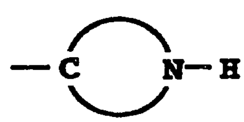


(VIIe)

wherein Q^1, Q^{2b} and R^{20} have the same meanings as described above and m2 stands for an integer of 2 to 6 and a group of the following formula:

[0259]

[Chemical formula 47]



represents a 5- or 6-membered heterocyclic group which may have a substituent)], thereby forming the corresponding urea derivative; or by reacting the amine of the formula (IIIa) with an isocyanate derivative or an isocyanate prepared from a carboxylic acid represented by any one of the formulas (IVa) to (IVd).

[0260]

When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, coupling reaction can be effected with a boric-acid-substituted aryl compound in the presence of a transition metal catalyst.

[0261]

When in the structure of Q^1 of the compound represented by the formula (Ib), an alkenyl group or boric-acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

[0262]

When in the structure of Q^1 of the compound represented by the formula (Ib), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound. When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained, it can be subjected to coupling reaction with an alkenyl compound in the presence of a transition metal catalyst,

whereby the compound of the formula (Ib) can be obtained. If the nitrogen atom of Q^{3b} of the compound (Ib) so obtained has been protected, the compound of the formula (Ia) can be obtained by deprotection as needed.

[0263]

Examples of the carboxylic acids of the following formulas (IVa) to (IVd) in an activated form include acid mixed acid anhydrides available by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate; acid halides such as acyl chloride prepared using an acid halide such thionyl chloride; active esters obtained by reacting with a phenol such as paranitrophenol or pentafluorophenyl-trifluoroacetate; active esters obtained by reacting with N-hydroxybenztriazole or N-hydroxysuccinimide; reaction products with 1-benzotriazolyloxy-(pyrrolidino)-phosphonium hexafluorophosphite, N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride which is usually employed for the peptide synthesis of amino acid, reaction products with diethyl cyanophosphonate (salting-in method) and reaction products with triphenylphosphine and 2,2'-dipyridylsulfide (Mukaiyama's method).

[0264]

The resulting carboxylic acid in an activated form is then reacted with the compound of the formula (IIIa) or salt thereof

generally in the presence of an appropriate base in an inert solvent at -78°C to 150°C, whereby the compound of the formula (Ib) can be obtained.

[0265]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium botoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0266]

Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; aromatic solvents such as benzene and toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. In addition to them, sulfoxide solvents such as dimethylsulfoxide and sulfolane and ketone solvents such as acetone and methyl ethyl ketone can be used if they are suited.

[0267]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) forms an amide bond, the alkylation of the nitrogen atom is carried out by reacting the compound (IIIa) with the compound represented by any one of the formulas (Va) to (Vd) in the presence of an appropriate base in an inert solvent at -78 to 150°C, whereby the compound of the formula (Ib) can be obtained. Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU).

[0268]

Examples of the inert solvent include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and amide solvents such as N,N-dimethylformamide.

[0269]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be obtained by reacting the compound of the formula (IIIa) with the carbonyl compound of any one of the formulas (VIa) to (VId) to form the corresponding imine, generally in an inert solvent, if

necessary in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride at -20 to 150°C; and then hydrogenating the resulting imine in an inert solvent in the presence of a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride or a catalytic reduction catalyst such as palladium-carbon catalyst at 10 to 110°C.

[0270]

Preferred examples of the inert solvent include carbon halides such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, benzene solvents such as toluene and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one.

[0271]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the reaction product of the compound of any one of the formulas (VIIa) to (VIId) containing a primary amine or the compound of the formula (VIIe) containing a secondary amine with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole can be acted on the compound of the formula (IIIa) to introduce it to the corresponding urea derivative. The derivative can be synthesized by reacting the primary amine compound of any one of the formulas (VIIa) to (VIId) or the secondary amine compound

of the formula (VIIe) and the compound of the formula (IIIa) with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole, successively in this order if necessary in the presence of a base, in an inert solvent.

[0272]

Examples of the inert solvent include halogen solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; benzene solvents such as toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

[0273]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is effected within a temperature range of from -70°C to 110°C.

[0274]

When the nitrogen atom of Q^{3b} of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can also be obtained by reacting the compound of the formula (IIIa) with an isocyanate derivative

in an inert solvent at -20 to 100°C.

[0275]

The isocyanate derivative can be synthesized by converting the carboxylic acid of the formula (IVa) into the corresponding acid halide by using an acid halide such as thionyl chloride or oxalyl chloride in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the resulting acid halide with sodium azide in an inert solvent such as tetrahydrofuran, chloroform or toluene at a temperature range of from 0 to 80°C, and then heating the reaction mixture at 20 to 100°C; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such as isobutyl chloroformate in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C to obtain the corresponding mixed acid anhydride, reacting the mixed acid anhydride with sodium azide within a temperature range of from 0 to 80°C and then heating the reaction mixture at 20 to 100°C; or by introducing the carboxylic acid of the formula (IVa) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the hydrazide with nitric acid or alkyl ester thereof to convert it into the corresponding acyl azide and then heating the resulting acyl azide in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide at 20 to 150°C.

[0276]

The compound of the formula (Ib) can also be prepared by reacting the carboxylic acid of the formula (IVa) with diphenylphosphoryl azide in the presence of a base such as triethylamine, in an inert solvent such as chloroform, tetrahydrofuran, toluene or N,N-dimethylformamide at a temperature range of 10 to 140°C and then reacting the reaction mixture with the amine of the formula (IIIa).

[0277]

When in the structure of Q^1 of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyoxy-substituted alkenyl group is contained, the compound can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (O), in a two-phase solvent such as benzene-water or toluene-water, amide solvent such as N,N-dimethylformamide or ether solvent such as tetrahydrofuran or dimethoxyethane, if necessary in the presence of sodium carbonate, sodium hydroxide, calcium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate at a temperature range of 20 to 150°C for 0.5 to 120 hours.

[0278]

When an alkenyl group or boric-acid-substituted alkenyl group is contained in the structure of Q^1 of the compound

represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group can be effected using a transition metal catalyst such as palladium acetate, if necessary in the presence of an appropriate base or cesium fluoride, in an amide solvent such as N,N-dimethylformamide, at a temperature range of 20 to 150°C for 0.5 to 120 hours. When a boric-acid-substituted aryl group is contained in the structure of Q^1 of the compound represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl derivative or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative can be effected. When a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained in the structure of Q^1 of the compound, coupling reaction of the compound with an alkenyl compound can be effected using a transition metal catalyst, whereby the compound of the formula (Ib) can be obtained.

[0279]

If the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (Ib) has been protected, the compound of the formula (Ia) can be obtained by deprotection as needed.

[0280]

<Synthesis of the compound represented by the formula (IIa)>

The sulfonic acid halide of the formula (IIa) can be synthesized in a known matter or by application thereof. The

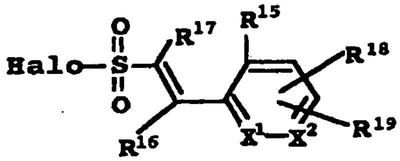
ordinarily employed synthesis process will be described below.

[0281]

Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-1a):

[0282]

[Chemical formula 48]

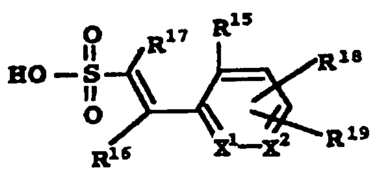


(IIa − 1a)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1, X^2 and Halo have the same meanings as described above] can be synthesized by any one of the various processes reported to date (The Chemistry of Sulfonic Acids Esters and their Derivatives, Edited by S. Patai and Z. Rappoport, 1991, John Wiley & Sons Ltd.), for example, halogenation of a sulfonic acid of the following formula (IIa-Ib):

[0283]

[Chemical formula 49]

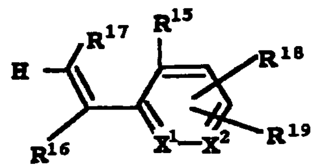


(IIa − 1b)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1 and X^2 have the same meanings as described above] or chlorosulfonylation of the unsaturated bond represented by the following formula (IIa-1c):

[0284]

[Chemical formula 50]



(IIa − 1c)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1 and X^2 have the same meanings as described above].

[0285]

For example, the sulfonic acid halide of the formula (IIa-Ia) can be obtained by reacting the sulfonic acid of the formula (IIa-Ib) with a thionyl halide in the presence of N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours. At this time, the reaction system may be diluted with an inert solvent such as dichloromethane, chloroform, carbon tetrachloride, N-methylpyrrolidin-2-one, dimethylsulfoxide or sulfolane.

[0286]

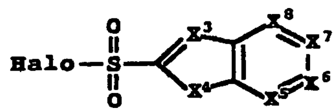
The sulfonic acid halide of the formula (IIa-Ia) can be obtained by reacting the unsaturated-bond-containing compound of the formula (IIa-Ic) with a thionyl halide or chlorosulfonic acid in an inert solvent such as N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours.

[0287]

Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-2a):

[0288]

[Chemical formula 51]

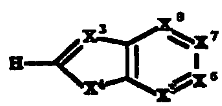


(IIa-2a)

[wherein X^3, X^4, X^5, X^6, X^7, X^8 and Halo have the same meanings as described above] can be obtained by the processes so far reported (Japanese Patent Application Laid-Open No. Sho 60-204760, Japanese Patent Application Laid-Open No. Sho 62-116575, Japanese Patent Application Laid-Open No. Hei 4-128266) or by application thereof, for example, by reacting the fused heterocycle represented by the following formula (IIa-2b):

[0289]

[Chemical formula 52]



(IIa-2b)

[wherein X^3, X^4, X^5, X^6, X^7 and X^8 have the same meanings as described above] with a base and then with sulfur dioxide and then reacting the reaction mixture with a halogenating agent.

[0290]

The compound of the formula (IIa-2b) is obtained, for example, by reacting the fused heterocycle of the formula (IIa-2b) with an appropriate base in an ether-type inert solvent at -78°C to 0°C, reacting the reaction mixture with sulfur dioxide at -78°C to 0°C, and then reacting with a halogenating

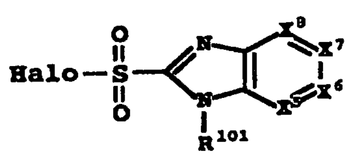
agent in an alkyl halide type inert solvent at -50°C to 50°C. Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium botoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and t-butyl lithium, dialkylaminolithium such as lithium diisopropylamide; organometallic bases of bissilylamine such as lithium bis(trimethylsilyl)amide. Examples of the ether-type inert solvent include diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and dioxane. Preferred examples of the halogenating agent include chlorine, bromine, phosphorus pentachloride, thionyl chloride, N-chlorosuccinimide and N-bromosuccinimide, while those of the alkyl halide type inert solvent include dichloromethane, chloroform and tetrachloroethane.

[0291]

Among the compounds represented by the formula (IIa-2a), the corresponding sulfonyl chloride of the compound represented by the following formula (IIa-2c):

[0292]

[Chemical formula 53]



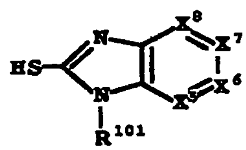
(IIa-2c)

[wherein R^{101}, X^5, X^6, X^7, X^8 and Halo have the same meanings as described above] can be obtained by reacting the compound of

the following formula (IIa-2d):

[0293]

[Chemical formula 54]



(IIa-2d)

[wherein R^{101}, X^5, X^6, X^7 and X^8 have the same meanings as described above] with halogen such as a chlorine gas at 0 to 30°C for 10 minutes to 6 hours in water or a mixed solvent of water with an organic carboxylic acid such as acetic acid.

[0294]

The reaction between the compound of the formula (IIa-2d) and halogen is carried out at 0 to 20°C usually in water or a 10 to 90% aqueous solution of acetic acid if necessary in the presence of a Lewis acid such as ferric chloride as a catalyst.

[0295]

<Reaction of a compound of the formula (Ia) with a compound of the formula (IIa)>

The compound of the formula (I) can be obtained generally by reacting the compound of the formula (Ia), which has been synthesized by the above-described process or the like, with the sulfonic acid halide of the formula (IIa) which has been synthesized by the above-described process or the like, in the presence of an appropriate base in an inert solvent at -78 to 150°C.

[0296]

The resulting compound of the formula (I) can be subjected to deprotection or chemical conversion of a substituent as needed.

[0297]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium botoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0298]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane and mixed solvents thereof.

[0299]

[Preparation Process-1-(1)]

When the nitrogen atom of Q^{3a} of the compound represented

by the formula (Ia), which is to be sulfonylated, constitutes a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali metal or an alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and usable examples of the solvent include, in addition to inert solvents, water, alcohol solvents such as ethanol and butanol and ester solvents such as ethyl acetate.

[0300]

[Preparation Process-1-(2)]

When the nitrogen atom of Q^{3a} of the compound represented by the formula (Ia), which is to be sulfonylated, constitutes an amide group, preferred examples of the base include alkoxides and hydrides of an alkali metal or an alkaline earth metal such as sodium ethoxide, potassium botoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, dioxane and N,N-dimethylformamide.

[0301]

[Preparation Process-2]

A process for preparing the sulfonyl derivative (I) by acylating the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):

$Q^{3a}-SO_2-Q^4$ (VIIIa)

[wherein Q^{3a} and Q^4 have the same meanings as described above] with any one of the carboxylic acids represented by the formulas (IVa) to (IVd):

[0302]

Q^1-Q^2-COOH (IVa)

[0303]

$Q^1-Q^{2b}-COOH$ (IVa)

[0304]

$Q^1-N(R^{20})-(CH_2)_{m1}-COOH$ (IVb)

[0305]

$Q^1-O-(CH_2)_{m1}-COOH$ (Ivc)

[0306]

$Q^1-S-(CH_2)_{m1}-COOH$ (Ivd)

[wherein Q^1, Q^2, Q^{2b}, Q^4, R^{20} and ml have the same meanings as described above] or the activated form thereof which are available by the process reported to date or the chemically usual process.

[0307]

The compound represented by the formula (VIIIa) can be

synthesized in various processes. Some of them will next be described.

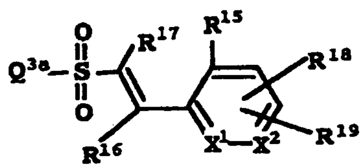
<<Synthesizing process of a compound represented by the formula (VIIIa)>>

<<Synthesizing process of a compound represented by the formula (VIIIa-Ia)>>

Among the compounds represented by the formula (VIIIa), the compound of the formula (VIIIa-Ia):

[0308]

[Chemical formula 55]



(VIIIa − 1a)

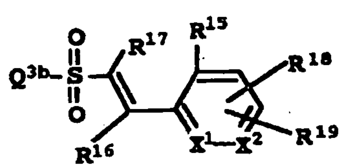
[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1, X^2 and Q^{3a} have the same meanings as described above] can be synthesized as described below.

[0309]

The compound of the following formula (VIIIa-Ib):

[0310]

[Chemical formula 57



(VIIIa − 1b)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1, X^2 and Q^{3b} have the same meanings as described above] can be obtained by sulfonylating the nitrogen atom of the primary amine, secondary amine or amide

of the compound of the formula (IIIa):

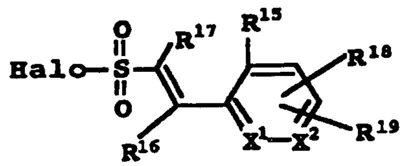
[0311]

Q^{3b}-H (IIIa)

[wherein Q^{3b} has the same meaning as described above] with a compound represented by the following formula (IIa-1a):

[0312]

[Chemical formula 56]



(IIa − 1a)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1, X^2 and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at -78 to 150°C.

[0313]

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium botoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and

diazabicyclo[5.4.0]undec-7-ene (DBU).

[0314]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

[0315]

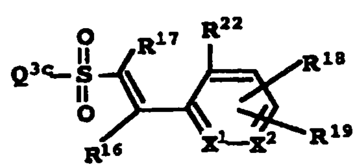
If the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (VIIIa-1b) has been protected, the compound of the formula (VIIIa-1a) can be obtained by deprotection as needed.

[0316]

The compound of the formula (VIIIa-1a) can be obtained by removing, in an appropriate manner, the protecting group from the nitrogen atom of the compound represented by the following formula (VIIIa-1c):

[0317]

[Chemical formula 58]



(VIIIa − 1c)

[wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X^1 and X^2 have the same meanings as described above, R^{22} represents

a hydrogen atom,

an alkyl group,

a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyl group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

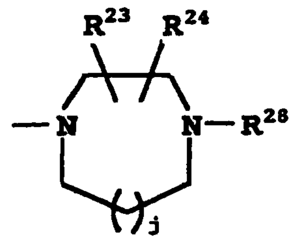
a dialkylaminoalkyloxy group,

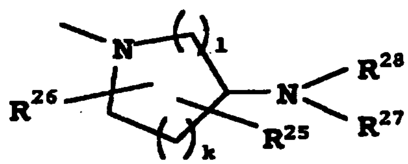
a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

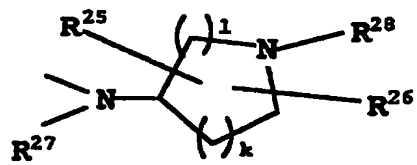
a dialkylaminocarbonylalkyloxy group or the like; and Q^{3c} represents any one of the following groups:

[0318]

[Chemical formula 59]







(wherein when the carbon atom to which R^{23}, R^{24}, R^{25} or R^{26} has been bonded is not adjacent to the nitrogen atom, R^{23}, R^{24}, R^{25} and R^{26} each independently represents:

a hydrogen atom,

an alkyl group,

a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyl group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonylalkyloxy group or the like; and when the carbon atom to which R^{23}, R^{24}, R^{25} or R^{26} has been bonded is adjacent to the nitrogen atom, R^{23}, R^{24}, R^{25} and R^{26} each independently represents:

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a dialkylaminoalkyloxy group or the like.

[0319]

R^{25} and R^{26}, as well as R^{23} and R^{24}, may be coupled together to form a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may

have a substituent.

[0320]

R^{27} represents:

an alkyl group,

a hydroxyalkyl group having the hydroxyl group protected,

a hydroxyalkylcarbonyl group having the hydroxyl group protected,

a hydroxyalkylsulfonyl group having the hydroxyl group protected,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarboylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having the amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group, or the like.

R^{26} and R^{27}, or R^{25} and R^{27} may be coupled together to form

a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

[0321]

R^{28} represents a tertiary butoxycarbonyl, benzyl or triphenylmethyl group which means a protecting group of the nitrogen atom, j and k each independently represents an integer of 0 or 1 and l stands for an integer of 1 to 3 with the proviso that the sum of k and l stands for an integer of 1 to 4.)]

[0322]

The compound represented by the formula (VIIIa-1c) can be obtained by reacting an amino compound which is available by the known process or application thereof and is represented by the following formula (IIIb):

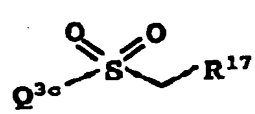
[0323]

Q^{3c}–H (IIIb)

[wherein Q^{3c} has the same meaning as described above] with an alkylsulfonic acid halide in the presence of an appropriate base; reacting the resulting sulfonamide represented by the following formula (IXa):

[0324]

[Chemical formula 60]



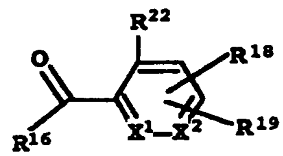
(IXa)

[wherein R^{17} and Q^{3c} have the same meanings as described above] with a carbonyl compound represented by the following formula

(XIa):

[0325]

[Chemical formula 61]

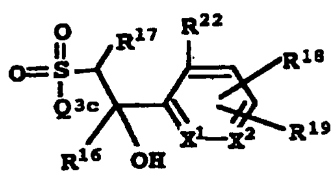


(XIa)

[wherein R^{16}, R^{18}, R^{19}, R^{22}, X^1 and X^2 have the same meanings as described above] in an inert solvent in the presence of an appropriate base to obtain the corresponding alcohol product represented by the following formula (XIIa):

[0326]

[Chemical formula 62]



(XIIa)

[wherein R^{16}, R^{17}, R^{18}, R^{19}, R^{22}, Q^{3c}, X^1 and X^2 have the same meanings as described above]; converting the alcohol moiety of the alcohol product (XIIa) into a methanesulfonyloxy group or the like in the presence of an appropriate base, or converting the alcohol moiety into a halogen atom by using a phosphorus halide or triphenylphosphine/carbon tetrahalide, thereby forming an eliminating group; and then eliminating methanesulfonic acid or hydrogen halide in the presence of an appropriate base.

[0327]

The sulfonamide compound of the formula (IXa) can be

obtained by reacting the amino compound of the formula (IIIb), which is available in a known process or by application thereof, with an alkylsulfonic halide which may have a substituent, in the presence of an appropriate base, in an inert solvent at -78 to 150°C.

[0328]

Examples of the base include carbonates of an alkali metal or alkaline earth metal, such as sodium carbonate and potassium carbonate and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0329]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Dimethylsulfoxide, sulfolane, acetone or the like can be used, though depending on the kind of the base employed.

[0330]

The alcohol compound of the formula (XIIa) can be obtained by reacting the sulfonamide of the formula (IXa) with a carbonyl compound of the formula (XIa) in the presence of an appropriate base in an inert solvent at -78 to 110°C.

[0331]

Examples of the base include hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium botoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and bissilylamine such as lithium bis(trimethylsilylamide; organometallic bases typified by dialkylaminolithium such as lithium diisopropylamide. Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane and dioxane.

[0332]

The compound of the formula (VIIIa-1c) can be obtained by treating the hydroxyl group of the alcohol product of the formula (XIIa) with a phosphorus halide such as phosphorus pentachloride or a triphenylphosphine-halogen complex such as triphenylphosphine dibromide at -20 to 110°C, if necessary in the presence of an appropriate base, for example, the carbonate of an alkali metal or alkaline earth metal, such as sodium carbonate or potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene or N,N-dimethylformamide, thereby obtaining the corresponding halide, and then eliminating the hydrogen halide from the resulting halide under basic conditions, for example, by treating at -78 to 150°C with a carbonate, alkoxide, hydroxide

or hydride of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or dialkylamine, e.g., lithiumbis(trimethylsilyl)amide, an organometallic base typified by dialkylaminolithium such as lithium diisopropylamide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

[0333]

The compound of the formula (VIIIa-1c) can also be obtained by treating the hydroxyl group of the alcohol product represented by the formula (XIIa) with an alkyl- or arylsulfonic acid chloride such as methanesulfonic acid chloride in the presence of an appropriate base, for example, a carbonate of an alkali metal or alkaline earth metal such as sodium carbonate or potassium carbonate or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as

dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene or N,N-dimethylformamide at -20 to 110°C to obtain the corresponding alkyl- or arylsulfonate derivative; and then eliminating the alkyl- or arylsulfonic acid from the resulting alkyl- or arylsulfonate derivative under basic conditions.

[0334]

Described specifically, the compound of the formula (VIIIa-1c) can be obtained by treating the resulting alkyl- or arylsulfonate derivative at -78 to 150°C in the presence of a carbonate, alkoxide, hydroxide or hydride of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or bissilylamine, e.g., lithium bis(trimethylsilyl)amide, an organometallic base typified by dialkylaminolithium such as lithium iisopropylamide, a bissilylamine base organometallic compound such as lithium bis(trimethylsilyl)amide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or

dimethylsulfoxide.

[0335]

The compound of the formula (VIIIa-1c) can also be obtained by treating the sulfonamide of the formula (IXa) with a silyl halide such as trimethylsilyl chloride in the presence of an appropriate base in an inert solvent to convert it to the corresponding silyl compound, reacting the resulting silyl compound with a carbonyl compound of the formula (XIa) in the presence of a base in an inert solvent and then treating the reaction product under acidic to basic aqueous conditions (Peterson's reaction).

[0336]

Described specifically, the compound of the formula (VIIIa-1c) can be obtained by treating the sulfonamide of the formula (IXa) with an alkylsilyl chloride such as trimethylsilyl chloride at -78 to 110°C in the presence of a hydride of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride or potassium hydride, an organometallic base such as alkyl lithium, e.g., n-butyl lithium or bissilylamine, e.g., lithium bis(trimethylsilyl)amide or an organometallic base typified by dialkylaminolithium such as lithium bis(trimethylsilyl)amide, for example, in a solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, to convert it to the corresponding silyl compound, condensing with the carbonyl compound of the formula (XIa) under the same conditions and then treating the

condensate under acidic to basic aqueous conditions.

[0337]

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-1c) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-1c) can be obtained.

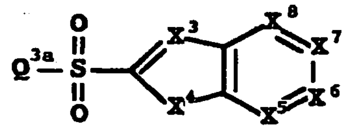
[0338]

<Synthesis of the compound represented by the formula (VIIIa-2a)>

Among the compounds represented by the formula (VIIIa), the compound of the formula (VIIIa-2a):

[0339]

[Chemical formula 63]



(VIIIa-2a)

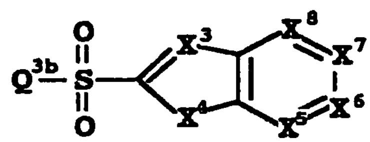
[wherein X^3, X^4, X^5, X^6, X^7, X^8 and Q^{3a} have the same meanings as described above] can be synthesized by the following process.

[0340]

Described specifically, the compound of the following formula (VIIIa-2b):

[0341]

[Chemical formula 65]



(VIIIa-2b)

[wherein X^3, X^4, X^5, X^6, X^7, X^8 and Q^{3b} have the same meanings as described above] can be obtained by sulfonylating the nitrogen atom of the primary or secondary amine or amide of the compound of the formula (IIIa):

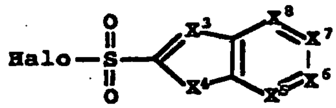
[0342]

Q^{3b}-H (IIIa)

[wherein Q^{3b} has the same meaning as described above] with a sulfonic acid halide represented by the following formula (IIa-2a):

[0343]

[Chemical formula 64]



(IIa-2a)

[wherein X^3, X^4, X^5, X^6, X^7, X^8 and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at -78 to 150°C.

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bissilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0344]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

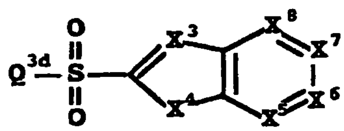
[0345]

When the nitrogen atom of Q^{3b} of the resulting compound represented by the formula (VIIIa-2b) has been protected, the compound of the formula (VIIIa-2a) can be obtained by carrying out deprotection as needed.

Alternatively, the compound of the formula (VIIIa-2a) can be obtained by removing, as needed in an appropriate manner, the protecting group of the nitrogen atom of Q^{3d} of the compound which is available by the below-described preparation process and is represented by the following formula (VIIIa-2c):

[0346]

[Chemical formula 66]

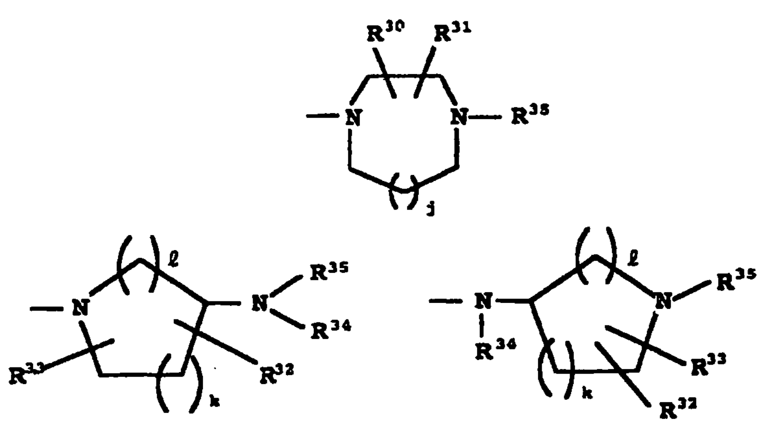


(VIIIa-2c)

[wherein X^3, X^4, X^5, X^6, X^7 and X^8 have the same meanings as described above and Q^{3d} means any one of the following groups:

[0347]

[Chemical formula 67]



(wherein, when the carbon atom to which each of R^{30}, R^{31}, R^{32} and R^{33} has been bonded is not adjacent to a nitrogen atom, R^{30}, R^{31}, R^{32} and R^{33} each independently represents

a hydrogen atom,

an alkyl group,

a hydroxyl group,

a hydroxyl group protected with a methoxymethyl or tetrahydropyranyl or the like group,

a hydroxyalkyl group,

a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl or tetrahydropyranyl or the like group,

an alkoxyl group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a monoalkylaminocarbonylalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonylalkyloxy group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a carbamoyl group,

a monoalkylcarbamoyl group,

a dialkylcarbamoyl group,

a carbamoylalkyl group,

a monoalkylcarbamoylalkyl group,

a dialkylcarbamoylalkyl group,

a pyrrolidinocarbonyl group,

a pyrrolidinocarbonylalkyl group,

a piperidinocarbonyl group,

a piperidinocarbonylalkyl group,

a morpholinocarbonyl group,

a morpholinocarbonylalkyl group,

a dialkylaminocarbonylalkyloxy group, or the like;

[0348]

when the carbon atom to which each of R^{30}, R^{31}, R^{32} and R^{33} has been bonded is adjacent to a nitrogen atom, R^{30}, R^{31}, R^{32} and R^{33} each independently represents

a hydrogen atom,

an alkyl group,

a hydroxyalkyl group having a hydroxy group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyalkyl group,

a dialkoxyalkyl gorup,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a carbamoyl group,

a monoalkylcarbamoyl group,

a carbamoylalkyl group,

a monoalkylcarbamoylalkyl group,

a pyrrolidinocarbonyl group,

a pyrrolidinocarbonylalkyl group,

a piperidinocarbonyl group,

a piperidinocarbonylalkyl group,

a morpholinocarbonyl group,

a morpholinocarbonylalkyl group,

a dialkylaminoalkyloxyalkyl group or the like;

[0349]

R^{30} and R^{31}, or R^{32} and R^{33} may be coupled together to form a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent;

R^{34} represents

an alkyl group,

a hydroxyalkyl group having a protected hydroxyl group,

a hydroxyalkylcarbonyl group having a protected hydroxyl group,

a hydroxyalkylsulfonyl group having a protected hydroxyl group,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,

an alkoxyalkylsulfonyl group,

an alkylcarbonyl group,

an alkylcarbonylalkyl group,

an alkylsulfonyl group,

an alkylsulfonylalkyl group,

an alkoxycarbonyl group,

an alkoxycarbonylalkyl group,

an alkoxycarbonylalkylcarbonyl group,

an alkoxycarbonylalkylsulfonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group or the like;

R^{32} and R^{34}, or R^{33} and R^{34} may be coupled together to form a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent;

[0350]

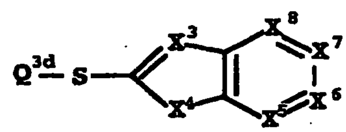
R^{35} represents an ordinarily employed protecting group for a nitrogen atom such as tertiary butoxycarbonyl group, benzyl group or triphenylmethyl group; j and k independently represents 0 or an integer of 1; and l stands for an integer of 1 to 3 with the proviso that the sum of k and l stands for an integer of 1 to 4)].

[0351]

The compound represented by the following formula (VIIIa-2d):

[0352]

[Chemical formula 69]



(VIIIa-2d)

[wherein X^3, X^4, X^5, X^6, X^7, X^8 and Q^{3d} have the same meanings as described above] can be obtained by reacting an amino compound, which is available in a known manner or by application thereof and is represented by the following formula (IIIc):

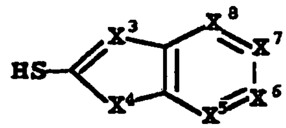
[0353]

Q^{3d}-H (IIIc)

[wherein Q^{3d} has the same meaning as described above] with a fused heterocyclic thiol compound represented by the following formula (IIa-2e):

[0354]

[Chemical formula 68]



(IIa-2e)

[wherein X^3, X^4, X^5, X^6, X^7 and X^8 have the same meanings as described above] in the presence of an appropriate base and oxidizing agent.

[0355]

The compound of the formula (VIIIa-2c) can be obtained by oxidizing the resulting compound of the formula (VIIIa-2d) in an inert solvent in the presence of an appropriate base.

[0356]

The compound of the formula (VIIIa-2d) can be obtained by reacting an amino compound, which is represented by the formula (IIIc) and is available in a known manner or by application thereof, with a thiol represented by the formula (IIa-2e) at -10 to 50°C in the presence of an appropriate base and oxidizing agent in water, an alcohol or dioxane or a mixed solvent thereof.

[0357]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide. Examples of the oxidizing agent include oxygen, chlorine, bromine, iodine and hypochlorous acid. The compound of the formula (VIIIa-2c) can be obtained by reacting the resulting compound of the formula (VIIIa-2d) with an inorganic oxidizing

agent such as potassium permanganate or hydrogen peroxide or an organic oxidizing agent such as 3-chloroperbenzoic acid at -30°C to 60°C in the presence of an appropriate base in water, alcohol or a mixed solvent thereof.

[0358]

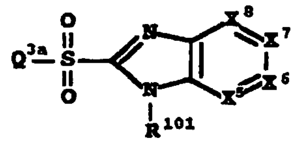
The protecting group of the nitrogen atom can be removed from the compound of the formula (VIIIa-2c) by an ordinarily employed process. Described specifically, when the nitrogen atom has been protected with a tertiary butoxycarbonyl group, the protecting group can be removed using an appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst. By deprotection as described above, the compound represented by the formula (VIIIa-2a) can be obtained.

[0359]

Among the compounds represented by the formula (VIIIa-2a), the compound of the following formula (VIIIa-2e):

[0360]

[Chemical formula 70]



(VIIIa-2e)

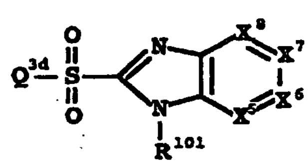
[wherein X^3, X^4, X^5, X^6, X^7, X^8, R^{101} and Q^{3a} have the same meanings as described above] can also be obtained by removing the protecting group from the nitrogen atom of Q^{3d} of the compound which is available by the below-described preparation process and is represented by the formula (VIIIa-2f).

[0361]

Described specifically, the compound of the following formula (VIIIa-2f):

[0362]

[Chemical formula 72]



(VIIIa-2f)

[wherein X^3, X^4, X^5, X^6, X^7, X^8, R^{101} and Q^{3d} have the same meanings as described above] can be obtained by reacting an amino compound which is available in a known manner or by the application thereof and is represented by the following formula (IIIc):

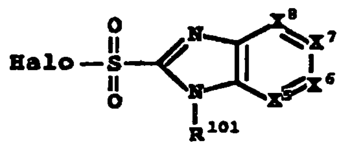
[0363]

Q^{3d}-H (IIIc)

[wherein Q^{3d} has the same meaning as described above] with an acid halide represented by the following formula (IIa-2c):

[0364]

[Chemical formula 71]



(IIa-2c)

[wherein X^3, X^4, X^5, X^6, X^7, X^8, R^{101} and Halo have the same meanings as described above].

[0365]

The compound of the formula (VIIIa-2f) can be obtained by reacting the compound of the formula (IIa-2d) with halogen such as chlorine gas at 0 to 30°C for 10 minutes to 6 hours in water or a mixed solvent of water with an organic carboxylic acid such as acetic acid, thereby forming the corresponding sulfonyl chloride; and then adding the resulting sulfonyl chloride to an amino compound of the formula (IIIc), which has been dissolved in an appropriate solvent, at -50 to 40°C.

[0366]

The reaction between the compound of the formula (IIa-2d) and halogen is carried out at 0 to 20°C, usually in water or a 10 to 90% aqueous solution of acetic acid, if necessary in the presence of a Lewis acid such as ferric chloride as a catalyst. As the halogen, a chlorine gas is used. The reaction

of the resulting acid chloride (IIa-2c) with the amine of the formula (IIIc) is carried out at -20 to 50°C in a solvent, for example, water, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform or acetone or a mixed solvent thereof, if necessary in the presence of a base, whereby the compound of the formula (VIIIa-2f) can be obtained. Specific examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0367]

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-2f) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be

removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl group can be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-2e) can be obtained.

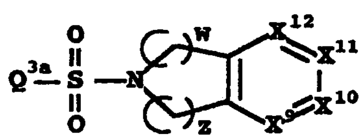
[0368]

<Synthesis of the compound of the formula (VIIIa-3a)>

Among the compounds of the formula (VIIIa), the compound of the following formula (VIIIa-3a):

[0369]

[Chemical formula 73]

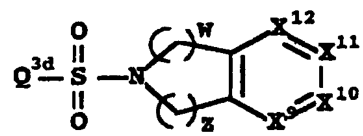


(VIIIa-3a)

[wherein X^9, X^{10}, X^{11}, X^{12}, Q^{3a}, w and z have the same meanings as described above] can be obtained by removing the protecting group from the nitrogen atom of Q^{3d} of the compound which is available by the below-described preparation process and is represented by the following formula (VIIIa-3b):

[0370]

[Chemical formula 74]



(VIIIa-3b)

[wherein X^9, X^{10}, X^{11}, X^{12}, Q^{3d}, w and z have the same meanings as described above].

[0371]

Described specifically, the compound represented by the following formula (XIV):

[0372]

$Q^{3d}-SO_2-NHCOOR^{60}$ (XIV)

[wherein R^{60} and Q^{3d} have the same meanings as described above] can be synthesized by reacting an amino compound represented by the following formula (IIIc):

[0373]

$Q^{3d}-H$ (IIIc)

[wherein Q^{3d} has the same meaning as described above] with a compound represented by the following formula (XIII):

$Cl-SO_2-NHCOOR^{60}$ (XIII)

[wherein R^{60} represents an easily removable group such as tertiary butyl, benzyl, paramethoxybenzyl or paranitrobenzyl], which has been obtained from chlorosulfonyl isocyanate and an alcohol, in the presence of an appropriate base in an inert solvent.

[0374]

The compound of the formula (VIIIa-3b) can be synthesized

by removing the protecting group on the nitrogen atom of the compound of the formula (XIV), thereby obtaining the compound represented by the following formula (XV):

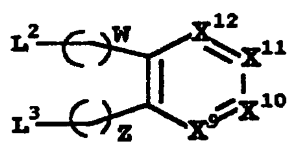
[0375]

$Q^{3d}-SO_2-NH_2$ (XV)

[wherein, Q^{3d} has the same meaning as described above] and then reacting the resulting compound of the formula (XV) with a compound represented by the following formula (IIa-3a):

[0376]

[Chemical formula 75]



(IIa-3a)

[wherein, X^9, X^{10}, X^{11}, X^{12}, w and z have the same meanings as described above, L^2 and L^3 each independently represents an eliminating group frequently employed in organic chemistry such as chlorine, bromine, iodine, methylsufonyloxy or paratoluenesulfonyloxy] in the presence of an appropriate base in an inert solvent.

[0377]

The reaction between the compounds of the formula (IIIc) and (XIII) is carried out at -70 to 100°C in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, benzene, toluene or acetone, or a mixed solvent thereof in the presence of a base

such as sodium carbonate, potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU), whereby the compound of the formula (XIV) can be obtained.

[0378]

The protecting group on the nitrogen atom of the compound represented by the formula (XIV) can be removed as described below. When the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the protecting group, the compound of the formula (XV) can be obtained.

[0379]

The reaction of the compound of the formula (XV) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C

in the presence of a base in a solvent, for example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, N,N-dimethylformamide, N-methylpyrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (VIII-3b) can be obtained. Examples of the base include sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0380]

The protecting group of the nitrogen atom of the compound represented by the formula (VIII-3b) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or

trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIII-3a) can be obtained.

<Reaction of any one of the compounds of the formulas (IVa) to (IVd) with the compound of the formula (VIIIa>

Examples of the carboxylic acid of each of the formulas (IVa) to (IVd) in an appropriate activated form include acid mixed acid anhydrides available by reacting the carboxylic acid of each of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate, thereby converting it into the corresponding acid anhydride, acid halides such as acyl chloride prepared by treating with an inorganic acid halide such thionyl chloride, phenols such as paranitrophenol, active esters obtained by reacting with pentafluorophenyl-trifluoroacetate, active esters obtained by reacting it with N-hydroxybenztriazole or N-hydroxysuccinimide, reaction products with N,N′-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride which is ordinarily employed in the synthesis of an amino acid, reaction products with diethyl cyanophosphonate (salting-in method) and reaction products with triphenylphosphine and 2,2′-dipyridylsulfide (Mukaiyama′s method).

[0381]

The resulting carboxylic acid in an activated form is reacted with the compound of the formula (VIIIa) at −78 to 150°C, usually in the presence of an appropriate base in an inert solvent, whereby the sulfonyl derivative of the formula (I) can be obtained.

[0382]

Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic basess typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bissilylamine such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0383]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

[0384]

[Preparation Process-2-(1)]

When the nitrogen atom of Q^{3a} of the compound represented by the below-described formula (VIIIa) to be acylated:

$Q^{3a}-SO_2-Q^4$ (VIIIa)

[wherein, Q^{3a} and Q^4 have the same meanings as described above] is a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and usable examples of the solvent include, in addition to inert solvents, alcohol solvents such as ethanol and butanol and ester solvents such as ethyl acetate.

[0385]

[Preparation Process-2-(2)]

When the nitrogen atom of Q^{3a} of the compound represented by the below-described formula (VIIIa) to be acylated:

$Q^{3a}-SO_2-Q^4$ (VIIIa)

[wherein Q^{3a} and Q^4 have the same meanings as described above] forms an amide bond, examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl

lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bissilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, dioxane and N,N-dimethylformamide.

[0386]

[Preparation Process-3]

A process for preparing, in the case the nitrogen atom of Q^{3a} of the compound represented by the following formula (VIIIa):

$$Q^{3a}\text{-}SO_2\text{-}Q^4 \qquad \text{(VIIIa)}$$

[wherein, Q^{3a} and Q^4 have the same meanings as described above] constitutes an amide, the sulfonyl derivative of the present invention by alkylating the nitrogen atom of the formula (VIIIa) with any one of the compounds represented by the following formulas (Va) to (Vd):

[0387]

$$Q^1\text{-}Q^{2b}\text{-}CHL^1R^{13} \qquad \text{(Va)}$$

[0388]

$$Q^1\text{-}N(R^{20})\text{-}(CH_2)_{m1}\text{-}CHL^1R^{13} \qquad \text{(Vb)}$$

[0389]

$$Q^1\text{-}O\text{-}(CH_2)_{m1}\text{-}CHL^1R^{13} \qquad \text{(Vc)}$$

[0390]

$$Q^1\text{-}S\text{-}(CH_2)_{m1}\text{-}CHL^1R^{13} \qquad \text{(Vd)}$$

[0391]

[wherein Q^1, Q^{2b}, R^{13}, R^{20}, ml and L^1 have the same meanings as described above].

[0392]

When the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) is a nitrogen atom of an amide bond, the sulfonyl derivative of the formula (I) can be synthesized by alkylating the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) with any one of the compounds of the formulas (Va) to (Vd). Described specifically, the sulfonyl derivative (I) can be obtained by reacting the compound of the formula (VIIIa) with any one of the compounds of the formulas (Va) to (Vd) at -78 to 150°C for 0.5 to 120 hours in the presence of an appropriate base in an inert solvent, thereby effecting alkylation of the nitrogen atom.

[0393]

Examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal, such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic bases typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic bases such as bissilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU). Preferred examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, toluene, dioxane and N,N-dimethylformamide.

[0394]

[Preparation Process-4]

A process for preparing, in the case where the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):

$$Q^{3a}-SO_2-Q^4 \qquad (VIIIa)$$

[wherein, Q^{3a} and Q^4 have the same meanings as described above] exists as a primary or secondary amine, the sulfonyl derivative (I) by forming the corresponding imine with any one of the carbonyl compounds represented by the following formulas (VIa) to (VId):

[0395]

$$Q^1-Q^{2b}-C(=O)R^{13} \qquad (VIa)$$

[0396]

$$Q^1-N(R^{20})-(CH_2)_{m1}-C(=O)R^{13} \qquad (VIb)$$

[0397]

$$Q^1-O-(CH_2)_{m1}-C(=O)R^{13} \qquad (VIc)$$

[0398]

$$Q^1-S-(CH_2)_{m1}-C(=O)R^{13} \qquad (VId)$$

[wherein Q^1, Q^{2b}, R^{13}, R^{20} and m1 have the same meanings as described above], followed by reduction.

[0399]

[0400]

When the nitrogen atom of Q^{3a} of the compound of the formula (VIIIa) constitutes an amine, the sulfonyl derivative of the formula (I) can be prepared by reacting the compound of the

formula (VIIIa) with any one of the carbonyl compounds of the formulas (VIa) to (VId) at -20 to 150°C for 0.5 to 120 hours, usually in an inert solvent, if necessary in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride, thereby forming the corresponding imine and then hydrogenating the resulting imine with a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride or a catalytic reduction catalyst such as palladium-carbon in an inert solvent at 10 to 110°C for 0.5 to 120 hours.

[0401]

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

[0402]

[Preparation Process-5]

A process for reacting, in the case where Q^{3a} of the compound represented by the following formula (VIIIa):

$$Q^{3a}-SO_2-Q^4 \qquad \text{(VIIIa)}$$

[wherein, Q^{3a} and Q^4 have the same meanings as described above] exists as a primary or secondary amine, the compound of the formula (VIIIa) with any one of the primary-amine-containing compounds represented by the following formulas (VIIa) to

(VIId):

[0403]

$Q^1-Q^{2b}-NH_2$ (VIIa)

[0404]

$Q^1-N(R^{20})-(CH_2)_{m2}-NH_2$ (VIIb)

[0405]

$Q^1-O-(CH_2)_{m2}-NH_2$ (VIIc)

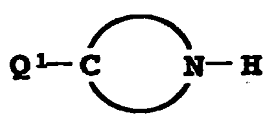
[0406]

$Q^1-S-(CH_2)_{m2}-NH_2$ (VIId)

or a secondary-amine-containing compound represented by the following formula (VIIe):

[0407]

[Chemical formula 76]

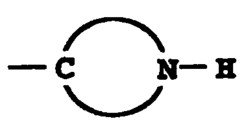


(VIIe)

[in the above-described formulas, Q^1, Q^{2b}, R^{20}, m2 and the group:

[0408]

[Chemical formula 77]



have the same meanings as described above] by using a reagent such as phosgene, triphosgene or carbonyldiimidazole, thereby forming the corresponding urea derivative.

[0409]

When Q^{3a} of the compound of the formula (VIIIa) constitutes an amine, the compound of the formula (VIIIa) is reacted with any one of the primary-amine-containing compounds represented by the formulas (VIIa) to (VIId) or the secondary-amine-containing compound represented by the formula (VIIe) and a reagent such as phosgene, triphosgene or 1,1′-carbonyldiimidazole to introduce it into the sulfonyl derivative of the present invention represented by the formula (I), which is to be an urea derivative.

[0410]

The synthesis can be carried out by successively reacting a reagent such as phosgene, triphosgene or 1,1′-carbonyldiimidazole with any one of the primary-amine-containing compounds of the formulas (VIIa) to (VIId) or the secondary-amine-containing compound of the formula (VIIe) and the compound of the formula (VIIIa), if necessary in the presence of a base, in an inert solvent. Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

[0411]

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate,

potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction may be conducted at a temperature range of from -70°C to 110°C.

[0412]

[Preparation Process-6]

A process for preparing a urea-containing sulfonyl derivative of the formula (I) by reacting, in the case where the nitrogen atom of Q^{3a} of the compound represented by the formula (VIIIa):

$$Q^{3a}-SO_2-Q^4 \qquad \text{(VIIIa)}$$

[wherein, Q^{3a} and Q^A have the same meanings as described above] exists as a primary or secondary amine, the amine of the formula (VIIIa) with a known isocyanate derivative ($Q^1-Q^{2b}-N=C=O$) [wherein, Q^1 and Q^{2b} have the same meanings as described above] or an isocyanate prepared from any one of the carboxylic acids represented by the following formulas (IVa) to (IVd):

[0413]

$$Q^1-Q^{2b}-COOH \qquad \text{(IVa)}$$

[0414]

$$Q^1-N(R^{20})-(CH_2)_{m1}-COOH \qquad \text{(IVb)}$$

[0415]

$$Q^1-O-(CH_2)_{m1}-COOH \qquad \text{(Ivc)}$$

[0416]

Q^1-S-$(CH_2)_{m1}$-COOH (Ivd)

[wherein Q^1, Q^{2b}, R^{20} and m1 have the same meanings as described above].

[0417]

When Q^{3a} of the compound represented by the formula (VIIIa) is an amine, the sulfonyl derivative of the formula (I) can be prepared by reacting the compound of the formula (VIIIa) with a known isocyanate derivative at -20 to 100°C for 0.5 to 120 hours in an inert solvent.

[0418]

The isocyanate derivative can be synthesized from any one of the carboxylic acids of the formulas (IVa) to (IVd). Described specifically, it can be obtained by introducing any one of the carboxylic acids of the formulas (IVa) to (IVd) into the corresponding acid halide with thionyl chloride, oxalyl chloride or the like, reacting the resulting acid halide with sodium azide at a temperature range of from 0 to 60°C in an inert solvent and then, heating the reaction mixture; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such as isobutyl chloroformate, reacting the resulting acid anhydride with sodium azide and then heating the reaction mixture; or introducing any one of the carboxylic acids represented by the formulas (IVa) to (IVd) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the resulting hydrazide with nitrous acid or alkyl

ester thereof to introduce it into the corresponding acyl azide and then heating at 20 to 150°C in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide.

[0419]

The sulfonyl derivative of the formula (I) can also be prepared by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with diphenylphosphorylazide at 10 to 100°C in the presence of a base such as triethylamine in an inert solvent and then reacting the reaction mixture with the amine of the formula (VIIIa).

[Preparation Process-7]

The compound represented by the following formula (XVI):

[0420]

Q^1-Q^2-T^1-Q^3-SO_2-NHCOOR^{60} (XVI)

[wherein, Q^1, Q^2, Q^3, R^{60} and T^1 have the same meanings as described above] can be synthesized by reacting, in the case where the nitrogen atom of Q^{3a} of the compound represented by the following formula (Ia) to be sulfonylated:

[0421]

Q^1-Q^2-T^1-Q^{3a} (Ia)

[wherein, Q^1, Q^2, Q^{3a} and T^1 have the same meanings as described above] exists as a primary or secondary amine, the compound of the formula (Ia) with a compound which is available from chlorosulfonyl isocyanate and an alcohol and is represented by the following formula (XIII):

$Cl-SO_2-NHCOOR^{60}$ (XIII)

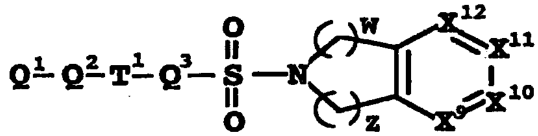
[wherein, R^{60} has the same meaning as described above] in the presence of an appropriate base in an inert solvent.

[0422]

The compound represented by the following formula (I-3a):

[0423]

[Chemical formula 79]



(I-3a)

[wherein, Q^1, Q^2, Q^3, T^1, X^9, X^{10}, X^{11}, X^{12}, w and z have the same meanings as described above], one of the compounds of the formula (I), can be synthesized by removing the protecting group on the nitrogen atom of the resulting compound (XVI), thereby obtaining a compound represented by the following formula (XVII):

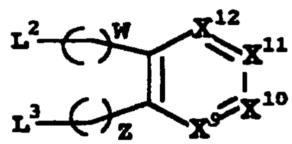
[0424]

$Q^1-Q^2-T^1-Q^3-SO_2-NH_2$ (XVII)

[wherein, Q^1, Q^2, Q^3 and T^1 have the same meanings as described above]; and then reacting the resulting compound of the formula (XVII) with a compound represented by the following formula (IIa-3a):

[0425]

[Chemical formula 78]



(IIa-3a)

[wherein, X^9, X^{10}, X^{11}, X^{12} L^2, L^3, w and z have the same meanings as described above] in an appropriate base in an inert solvent.

The reaction between the compound of the formula (Ia) and the compound of the formula (XIII) to synthesize the compound of the formula (XVI) is effected at -70 to 100°C in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, or a solvent such as benzene, toluene or acetone or a mixed solvent thereof and in this reaction, usable examples of the base include sodium carbonate, potassium carbonate and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0426]

The protecting group on the nitrogen atom of the compound of the formula (XVI) can be removed as described below. When the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or

paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the protecting group, the compound of the formula (XVII) can be obtained.

[0427]

The reaction of the compound of the formula (XVII) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C in the presence of a base in a solvent, for example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, N,N-dimethylformamide, N-methylpyrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (I-3a), one of the compounds of the formula (I), can be obtained.

[0428]

Examples of the base include sodium carbonate, potassium carbonate, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0429]

From the compound of the formula (I-3a), it is possible to eliminate the protecting group in an ordinarily employed process if necessary.

[0430]

[Preparation Process-8]

A process for synthesizing a sulfonyl derivative represented by the following formula (I):

$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^3\text{-}SO_2\text{-}Q^4 \qquad (I)$$

[wherein, Q^1, Q^2, Q^3, Q^4, T^1 have the same meanings as described above] by coupling reaction using a transition metal catalyst.

[0431]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, it can be subjected to coupling reaction with a boric-acid-substituted aryl compound in the presence of a transition metal catalyst.

[0432]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), an alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

[0433]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound.

[0434]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained, the sulfonyl derivative of the formula (I) can be obtained by coupling with an alkenyl compound in the presence of a transition metal catalyst. The sulfonyl derivative of the formula (I) thus obtained may be deprotected as needed.

[0435]

When in the structure of Q^1 of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, it can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (O), in a two-phase solvent such as benzene-water or toluene-water, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran or dimethoxyethane,

in the presence of a base such as sodium carbonate, sodium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate or a neutral salt such as cesium fluoride at a temperature range of 20 to 150°C for 0.5 to 120 hours.

[0436]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative.

[0437]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), an alkenyl group or boric-acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group by using a transition metal catalyst such as palladium acetate, in the presence of an appropriate base, in an amide solvent such as N,N-dimethylformamide at a temperature range of from 20 to 150°C for 0.5 to 120 hours.

[0438]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted

aryl derivative or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative.

[0439]

When in the structure of Q^1 of the sulfonyl derivative represented by the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group, it can be subjected to coupling reaction with an alkenyl compound by using a transition metal catalyst. By the above-described process, the sulfonyl derivative of the formula (I) can be obtained. By deprotection of the resulting sulfonyl derivative of the formula (I) as needed, the sulfonyl derivative of the formula (I) having a changed substituent can be obtained.

[0440]

[Preparation Process-9]

A process for preparing an amidoxime type sulfonamide product:

When T^1-Q^3 of the sulfonyl derivative represented by the following formula (I):

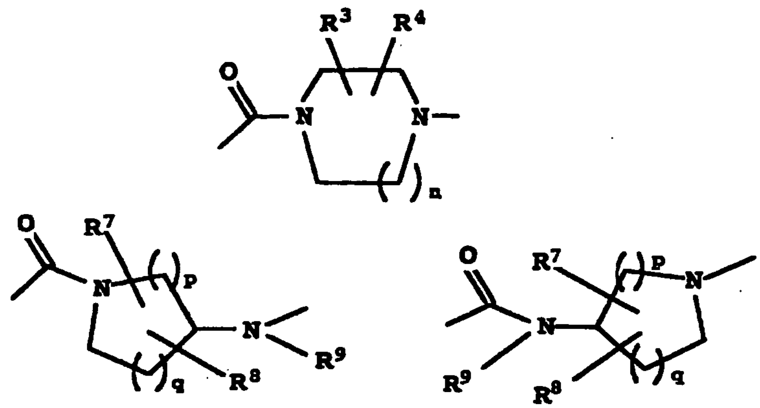
[0441]

$$Q^1\text{-}Q^2\text{-}T^1\text{-}Q^3\text{-}SO_2\text{-}Q^4 \qquad \text{(I)}$$

[wherein Q^1, Q^2, Q^3, Q^4 and T^1 have the same meanings as described above] represents any one of the following formulas:

[0442]

[Chemical formula 80]



[wherein R^3, R^4, R^7, R^8 and R^9 have the same meanings as described above, n stands for an integer of 1 or 2, p stands for an integer of 1 to 3 and q stands for an integer of 0 to 3 with the proviso that the sum of p and q stands for an integer of 3 or 4] and none of amine-, alkylamine-, amido-, hydroxyl- and carboxylic-acid-containing substituents exist on R^3, R^4, R^7, R^8, R^9 or a substituent replaceable therewith in Q^1, Q^2 and Q^3 of the formula (I), the sulfonyl derivative of this type represented by the formula (I) can be obtained by reacting the sulfonyl derivative of the formula (I) with a halogenating agent such as phosphorous oxychloride or phosphorus pentachloride or an alkylating agent such as Meerwein reagent at -30 to 140°C, if necessary in an inert solvent, for example, a halogen solvent such as chloroform at 0 to 80°C, to convert the derivative into the corresponding imino chloride or imino ether and then, reacting the resulting imino chloride or imino ether with hydroxylamine, alkoxyamine which may have a substituent or salt thereof at 0 to 80°C, preferably at 20 to 60°C, if necessary in the presence of a base catalyst.

[0443]

Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and aromatic solvents such as benzene and toluene. Among them, the alkyl halide solvents are particularly preferred. Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic bases typified by an alkyl lithium such as n-butyl lithium and a dialkylamino lithium such as lithium diisopropylamide; organometallic bases such as bissilylamine, e.g., lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0444]

[Preparation Process-10]

N-oxide formation

When in the sulfonyl derivative of the formula (I), there exists a nitrogen-containing heterocyclic aromatic ring or aliphatic tertiary amine on Q^1, Q^2, Q^3, Q^A or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula

(I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at -40 to 60°C for 0.5 to 120 hours preferably -20 to 20°C in a solvent such as water or acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, whereby the sulfonyl derivative of the formula (I) can be obtained as an N-oxide derivative.

[0445]

[Preparation Process-11]

Quaternization of a nitrogen atom

When in the sulfonyl derivative of the formula (I), there exists a nitrogen-containing heterocyclic aromatic group or aliphatic tertiary amine on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula (I) is reacted with an alkyl halide such as methyl iodide or ethyl iodide in an ether solvent such as 1,2-dimethoxyethane or dioxane, an aromatic solvent such as benzene or toluene, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidin-2-one or a sulfoxide solvent such as dimethyl sulfoxide or sulfolane at -10 to 150°C, preferably 0 to 80°C, whereby the sulfonyl derivative of the formula (I) can be obtained as a quaternary amino product.

[0446]

[Preparation Process-12]

Sulfoxide or sulfone formation

When in the sulfonyl derivative of the formula (I), a sulfur-containing hetero ring or aliphatic thioether exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, the sulfonyl derivative of the formula (I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at −40 to 60°C for 0.5 to 120 hours, preferably −20 to 20°C in a solvent such as water or acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, whereby the sulfonyl derivative (I) can be obtained in the form of sulfoxide or sulfone.

[0447]

[Preparation Process-13]

Amidino formation-1

When in the sulfonyl derivative of the formula (I), a nitrile group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be converted into an amidino group by an ordinarily employed process. The amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by allowing an equal amount to large excess of a C_{1-4} alcohol such as methanol, ethanol or propanol to act on the sulfonyl derivative of the formula (I) at −10 to 60°C for 3 to 120 hours in an aliphatic ether solvent such as diethyl ether,

an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene or a mixed solvent thereof in the presence of a hydrogen halide such as hydrogen chloride or hydrogen bromide, thereby converting it to the corresponding imino ether; then reacting the resulting imino ether product with ammonium, a monoalkylamine which may have a substituent or a dialkylamine which may have a substituent, or a carbonate or acetate thereof at -10 to 140°C for 0.5 to 200 hours in a C_{1-4} alcohol such as ethanol or propanol, an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform, an aprotic solvent such as benzene, a solvent such as N,N-dimethylformamide or dimethylsulfoxide or a mixed solvent thereof, preferably at -8 to 30°C for 10 to 96 hours in ethanol.

[0448]

[Preparation Process-14]

Amidino formation-2

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on Q^1, Q^2, Q^3, Q^A or T^1 or a substituent replaceable therewith, it can be converted into a substituted amidino group by an ordinarily employed process.

[0449]

Described specifically, the amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by reacting the sulfonyl derivative of the formula (I) with an imino ether, imino chloride or salt thereof, which has been

synthesized from an amide compound or nitrile compound, in an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene, or a mixed solvent thereof, if necessary in the presence of a base catalyst, at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0450]

[Preparation Process-15]

N-nitrile formation

When in the sulfonyl derivative of the formula (I), a primary or secondary amine group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be cyanated by an ordinarily employed process.

[0451]

For example, the sulfonyl derivative of the formula (I) is reacted with cyan bromide in an alcohol solvent such as methanol, ethanol or propanol in the presence of a salt such as sodium acetate or a base at -10 to 110°C, preferably 0 to 60°C, whereby the sulfonyl derivative (I) having on the nitrogen

atom thereof a nitrile group can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0452]

[Preparation Process-16]

Amidoxime or carboxamido-O-alkyloxime introduction

When in the sulfonyl derivative of the formula (I), a nitrile group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be converted into an amidoxime or carboxamido-O-alkyloxime group by an ordinarily employed process.

[0453]

For example, the sulfonyl derivative of the formula (I) is reacted with hydroxylamine or an alkoxyamine which may have a substituent, or salt thereof in an alcohol solvent such as methanol, ethanol or propanol, an ether solvent such as diethyl ether or tetrahydrofuran, a halogenated hydrocarbon such as chloroform or dichloromethane, an aprotic solvent such as toluene, an amide solvent such as N,N-dimethylformamide or a solvent such as dimethylsulfoxide, or a mixed solvent thereof at -10 to 110°C, preferably 0 to 60°C, if necessary in the

presence of a base catalyst, whereby the sulfonyl derivative of the formula (I) having an amidoxime or carboxamido-O-alkyloxime group can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0454]

[Preparation Process-17]

Guanidino introduction

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a substituted or unsubstituted guanidino group by an ordinarily employed process.

[0455]

For example, the sulfonyl derivative of the formula (I) having a primary or secondary amino group is reacted with N,N'-di(tert-butoxy)carbonylthiourea and N,N'-dicyclohexylcarbodiimide as a condensing agent in an aliphatic ether solvent such as diethyl ether, a halogenated hydrocarbon such as chloroform or dichloromethane or an aprotic solvent such as benzene, or a mixed solvent thereof at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours, if

necessary in the presence of a base catalyst, and then, as usual, the tertiary butoxycarbonyl group is removed, whereby the sulfonyl derivative of the formula (I) as a guanidino compound can be synthesized. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[0456]

[Preparation Process-18]

Deprotection from the protected nitrogen atom

When in the sulfonyl derivative of the formula (I), an acylamino or alkoxycarbonylamino group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, an amino-containing derivative can be obtained by subjecting the derivative to hydrolysis at 0 to 80°C in a solvent such as water, a lower alcohol or tetrahydrofuranm, or a mixed solvent thereof in the presence of a base such as an alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide. The nitrogen atom to which an acyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl has been bonded can be converted into a nitrogen-hydrogen bond by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric

acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof in a solvent such as water, an alcohol solvent such as methanol, an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene and removing the acyl type protecting group from the nitrogen atom at 0 to 80°C.

[0457]

The nitrogen atom to which an arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para(ortho)-nitrobenzyloxycarbonyl has been bonded can be converted into a nitrogen-hydrogen bond by removing the arylmethoxycarbonyl group from the protected nitrogen atom through hydrogenolysis in the presence of a palladium-carbon catalyst in a solvent such as water, an alcohol solvent such as methanol or ethanol, an ester solvent such as ethyl acetate, an ether solvent such as diethyl ether or tetrahydrofuran, or a solvent such as acetic acid or N,N-dimethylformamide, or a mixed solvent thereof. The nitrogen atom to which a silyl type protecting group such as trimethylsilyl or tertiary butyl dimethylsilyl has been bonded can be converted into a nitrogen-hydrogen bond by reacting with hydrochloric acid or a hydrofluoride such as tetrabutylammonium fluoride at 0 to 80°C in an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as

tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene, thereby removing the silyl group from the protected nitrogen atom. The nitrogen atom to which a benzyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the benzyl group through the catalytic reduction at 0 to 80°C with a palladium-carbon catalyst or the like in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The nitrogen atom to which a triphenylmethyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the triphenylmethyl group through the catalytic reduction with a palladium-carbon catalyst or the like at 0 to 80°C in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The removal of the triphenylmethyl group and conversion into a nitrogen-hydrogen bond can also be carried out by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or a combination thereof at 0 to 80°C.

[0458]

[Preparation Process-19]

Ester hydrolysis

When in the sulfonyl derivative of the formula (I), an alkoxycarbonyl group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent

replaceable therewith, in the case of a methyl or ethyl ester, the alkoxycarbonyl group can be converted into the corresponding carboxylic acid by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide. In the case of a tertiary butyl ester, the tertiary butyl group can be removed by treating with trifluoroacetic acid or hydrochloric acid, while in the case of an arylmethyl type ester such as benzyl, the carboxylic acid can be obtained by removing the arylmethyl group by hydrogenolysis in the presence of a palladium-carbon catalyst. Conversion from an ester group to a carboxylic acid residue can be effected using potassium trimethylsilanolate.

[0459]

[Preparation Process-20]

When in the sulfonyl derivative of the formula (I), an acyloxy, arylmethyloxy, silylether, methoxymethyl or tetrahydropyranyl group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, the acyl group such as alkanoyl or aroyl can be removed by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide; or alternatively can be removed by reacting with an organic base such as ammonia or methylamine. The arylmethyl type protecting group can be removed by the hydrogenolysis with a palladium-carbon catalyst. The silylether group such as tertiary butyl dimethylsilyl can

be removed by a hydrofluoride salt such as tetrabutylammonium fluoride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid or hydrochloric acid.

[0460]

[Preparation Process-21]

When in the sulfonyl derivative of the formula (I), an amino group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be acylated by an ordinarily employed process which uses an acyl halide or activated carboxylic acid. Alternatively, it can be alkylated by reductive alkylation or the like process. The sulfonyl derivative of the formula (I) which is an urea derivative can be prepared by sulfonylation through sulfonic acid chloride or by reacting with isocyanate or carboxylic-acid-derived isocyanate.

[0461]

[Preparation Process-22]

When in the sulfonyl derivative of the formula (I), a carboxyl group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a carbamoyl, alkylcarbamoyl or dialkylcarbamoyl group by an ordinarily employed active ester method or mixed acid anhydride method and then converted into a hydroxyl or aldehyde group by reduction. The resulting hydroxyl or aldehyde group can be subjected to conversion of a functional group, such as ether bond formation, conversion into an amino group or conversion into an alkylamino group by the process ordinarily employed in organic chemistry.

The carboxyl group, after conversion into its ester or mixed acid anhydride directly or by the usual process, is reduced, whereby the corresponding alcohol can be obtained.

[0462]

[Preparation-23]

Formation of phenol

When in the sulfonyl derivative of the formula (I), an aryl-substituted methoxy group exists on Q^1, Q^2, Q^3, Q^4 or T^1 or a substituent replaceable therewith, it can be converted into a hydroxyl group by removing the methyl group using thylsilyl iodide at -78 to 110°C in an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride or a benzene solvent such as toluene, or at -78 to 110°C in a Lewis acid such as aluminum chloride, phosphorus tribromide or boron trifluoride, an alkyl halide solvent or an ether solvent.

[0463]

[Preparation process-24]

Conversion of a halogen atom into an alkynyl group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic ring substituted with

chlorine, bromine or iodine, such a halogen atom can be converted into an acetylene group by reacting with a silylacetylene compound in the presence of a transition metal catalyst.

[0464]

The conversion of chlorine, bromine or iodine into a silylacetylene group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with a silylacetylene such as trimethylsilylacetylene by using palladium acetate and triphenylphosphine at a temperature range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of a base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0465]

The silyl group can be removed from the resulting silylacetylene compound by treating the compound with a base such as potassium carbonate, potassium bicarbonate or sodium hydroxide in a solvent, for example, an alcohol solvent such

as methanol, an ether solvent such as tetrahydrofuran, water, or a mixed solvent thereof.

[0466]

[Preparation Example-25]

Conversion of a halogen atom into a nitrile group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic ring substituted with chlorine, bromine or iodine, such a halogen atom can be converted into a nitrile group by reacting with zinc cyanide in the presence of a transition metal catalyst. The conversion of chlorine, bromine or iodine into a nitrile group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with zinc cyanide by using

a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (O) at a temperature range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of an appropriate base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0467]

[Preparation process-26]

Conversion of a halogen atom into a trifluoromethyl group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) contains chlorine, bromine or iodine as a substituent, such a halogen atom can be converted into a trifluoromethyl group by reacting the compound with a trifluoromethylating reagent in the presence of a metal catalyst. Described specifically, the conversion of chlorine, bromine or iodine into a trifluoromethyl group can be effected by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the

formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) containing chlorine, bromine or iodine as a substituent, with a trifluoromethylating reagent such as methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of a metal catalyst such as copper iodide at a temperature range of from 0 to 150°C for 0.5 to 120 hours in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[0468]

[Preparation process-27]

Conversion of a nitrile group into a tetrazole group

When the compound of the formula (I) has a nitrile group as a substituent, it can be converted into the compound of the formula (I) having a tetrazole group by reacting the former with sodium azide or trimethylsilyl azide at 0 to 170°C in the presence of trimethylaluminum or di-n-butyltin oxide in a benzene solvent such as benzene or toluene.

[0469]

[Preparation process-28]

Conversion of an amidino group into an alkoxycarbonylamidino group

When the compound of the formula (I) contains an amidino group, it can be converted into the compound of the formula (I) containing an alkoxycarbonylamidino group by reacting the former with a reagent, for example, an acid chloride such as alkyl chlorocarbonate or alkyl p-nitrobenzylcarbonate at -78 to 100°C in the presence of a base in an alkyl halide solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran.

[0470]

Examples of the base include sodium carbonate, potassium carbonate, pyridine, 2,6-lutidine, 4-dimethylaminopyridine, diazabicyclo[5.4.0]undec-7-en (DBU).

[0471]

The sulfonyl derivative of the formula (I) according to the present invention, salt thereof or solvate thereof has peculiar and excellent FXa inhibitory activity and is therefore useful as a coagulation suppressor or a preventive and/or remedy for thrombosis or embolism.

[0472]

The sulfonyl derivative of the present invention exhibits effects even by the oral administration so that it can be administered either orally or parenterally. The dose of the sulfonyl derivative can be changed as needed depending on the symptom, age, weight and/or the like of a patient. In general, it is necessary to administer the derivative in an amount of

1 to 1000 mg/day, preferably 5 to 300 mg/day per adult. Although no particular limitation is imposed on the dosage form, examples include tablets, capsules, powders, granules, suspensions, syrups and dry syrups. The derivative together with ordinarily employed additives such as excipient, lubricant or binder can be formulated into the above-described dosage forms in accordance with the known formulation technique.

[0473]

No particular limitation is imposed on the dosage form in the case of parenteral administration but examples include ointments, plasters, injections and suppositories. As an injection, the derivative may be administered subcutaneously or intravenously or by intravenous drip in an amount of 0.1 to 100 mg/day, preferably 0.5 to 30 mg/day per adult.

[0474]

The sulfonyl derivatives of the present invention exhibit anticoagulant action based on excellent FAX inhibitory action. Accordingly, the sulfonyl derivative of the present invention can treat or prevent various diseases caused by thrombosis or embolism, for example, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis and disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of thrombus upon extracorporeal circulation and blood coagulation upon blood collection without

acting on platelets.

[0475]

The present invention will hereinafter be described more specifically by Referential Examples, Examples and Tests. It should however be borne in mind that the present invention is not limited to or by them.

[0476]

[Examples]

The sulfonyl derivative of the present invention and preparation process therefor will next be described specifically. Incidentally, the starting compounds for the sulfonyl derivative of the present invention contain novel compounds and such compounds and preparation process therefor will be described in Referential Examples.

[0477]

Upon preparation of the compound, Merck Silica Gel 60 or Yamazen Silica Gel for moderate pressure liquid chromatography were employed for silica gel column chromatography.

[0478]

In the nuclear magnetic resonance spectrum (NMR), tetramethylsilane was used an internal standard.

[0479]

[Referential Example 1]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride and trifluoroacetate

In dichloromethane (20 ml), tert-butyl 1-piperazine carboxylate (856 mg) was dissolved. To the resulting solution, triethylamine (0.77 ml) and 6-chloro-2-naphthylsulfonylchloride (WO96/10022) (1.20 g) were added, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with 1N hydrochloric acid. The organic layer extracted was dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in saturated ethanol hydrochloride (10 ml), followed by concentration under reduced pressure and washing with ethyl acetate, whereby the hydrochloride (1.62 g, quant.) of the title compound was obtained as a colorless solid.

[0480]

^{1}H-NMR (DMSO-d_6) δ: 3.1-3.4(8H,m), 7.75(1H,dd,J=8.8,2.0Hz), 7.86(1H,dd,J=8.8,1.5Hz), 8.22(1H,d,J=8.8Hz), 8.26-8.32(2H,m), 8.56(1H,s), 8.63(2H,br s).

MS (FAB) m/z: 311 [$(M+H)^+$, Cl^{35}], 313 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{14}H_{15}ClN_2O_2S \cdot HCl \cdot 0.1H_2O$

Calculated: C, 48.17; H, 4.68, Cl, 20.31; N, 8.03; S, 9.19.

Found: C, 47.91; H, 4.68; Cl, 20.41; N, 7.80; S, 9.21.

Instead of the saturated ethanol hydrochloride, treatment was carried out using trifluoroacetic acid, whereby the trifluoroacetate was obtained.

Elementary analysis for $C_{14}H_{15}ClN_2O_2S \cdot CF_3CO_2H$

Calculated: C, 45.24; H, 3.80, Cl, 8.35; F, 13.42; N, 6.59; S, 7.55.

Found: C, 44.84; H, 3.80; Cl, 8.27; F, 13.72; N, 6.29; S, 7.50.

[0481]

[Referential Example 2]

4-(4-Pyridyl)benzoic acid hydrochloride

At room temperature, 4-bromopyridine hydrochloride (11.7 g) and 4-carboxyphenylboronic acid (10.0 g) were dissolved in toluene (250 ml) and water (250 ml). To the resulting solution, tetrakis(triphenylphosphine)palladium (O) (5.00 g) and anhydrous sodium carbonate (25.4 g) were added successively, followed by refluxing under heat at 120°C for 19 hours. After cooling to room temperature, the reaction mixture was added with ethyl acetate and water, whereby the water layer was collected. The organic layer was extracted twice with water. All the water layers so obtained were combined and to the resulting solution, concentrated hydrochloric acid was added to make it acidic, followed by washing with ethyl acetate again. The solvent was distilled off from the water layer until it decreased to 100 ml. The colorless solid so precipitated was collected by filtration and dried under reduced pressure, whereby the title compound (8.37 g, 59%) was obtained.

[0482]

^{1}H-NMR (DMSO-d_6) δ: 8.11 (2H,d,J=8.8Hz), 8.14(2H,d,J=8.8Hz),

8.35(2H,d,J=6.6Hz), 8.97(2H,d,J=6.6Hz).

Elementary analysis for $C_{12}H_9NO_2 \cdot HCl \cdot 0.3H_2O$

Calculated: C, 59.79; H, 4.43, N, 5.81

Found: C, 59.87; H, 4.35; N, 5.53.

MS (FAB) m/z: 200 $(M+H)^+$.

[0483]

[Referential Example 3]

1-tert-Butoxycarbonyl-4-[4-(4-pyridyl)benzoyl]piperazine

In N,N-dimethylformamide (40 ml), 4-(4-pyridyl)benzoic acid hydrochloride (654 mg) and tert-butyl 1-piperazinecarboxylate (569 mg) were suspended. To the resulting suspension, 1-hydroxybenzotriazole (374 mg) and N-methylmorpholine (336 µl) were added. The resulting mixture was ice cooled, followed by the addition of 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (796 mg). After stirring at room temperature for 7 hours, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (2% methanol - dichloromethane), followed by washing with hexane, whereby the title compound (905 mg, 89%) was obtained.

[0484]

^1H-NMR ($CDCl_3$)δ: 1.48(9H,s), 3.40-3.91(8H,m), 7.51(2H,d,J=5.9Hz), 7.53(2H,d,J=8.1Hz), 7.69(2H,d,J=8.1Hz), 8.69(2H,d,J=5.9Hz).

Elementary analysis for $C_{21}H_{25}N_3O_3$

Calculated: C, 68.64; H, 6.86, N, 11.44.

Found: C, 68.48; H, 6.84; N, 11.17.

[0485]

[Referential Example 4]

1-[4-(4-Pyridyl)benzoyl]piperazine ditrifluoroacetate

In dichloromethane (30 ml), 1-tert-butoxycarbonyl-4-[4-(4-pyridyl)benzoyl]piperazine (944 mg) was dissolved. Under ice cooling, trifluoroacetic acid (30 ml) was added to the resulting solution, followed by stirring at room temperature for one hour. The solvent was distilled off. Tetrahydrofuran was added to the residue to solidify the same, whereby the title compound (1.28 g, 100%) was obtained as a colorless amorphous solid.

[0486]

^{1}H-NMR (DMSO-d_6) δ: 3.1-3.3(4H,br s), 3.5-4.0(4H,m), 7.65(2H,d,J=7.8Hz), 7.95-8.05(4H,m), 8.79(2H,d,J=5.4Hz), 8.95-9.10(1H,br s)

[0487]

[Referential Example 5]

4-tert-Butoxycarbonyl-2-ethoxycarbonyl-1-[4-(4-pyridyl)benzoyl]piperazine

In toluene (150 ml), 1,2-dibromopropionic acid (58.0 g) was dissolved. To the resulting solution, a solution of N,N'-dibenzylethylenediamine (53.5 g) and triethylamine (53 ml) in toluene (toluene: 50 ml) was added dropwise under ice cooling. Toluene (100 ml) was added again to the reaction

mixture, followed by stirring at room temperature for 14 hours, addition of toluene (100 ml) again and stirring at 60 to 80°C for 4 hours. The insoluble matter was filtered off. The filtrate was washed with water and dried over anhydrous potassium carbonate. The solvent was then distilled off under reduced pressure. The residue was dissolved in acetic acid (200 ml). To the resulting solution, 10% palladium carbon (water content: about 50%, 40 g) was added, followed by catalytic reduction under 4 atmospheric pressure for 4 hours. The catalyst was filtered off and the filtrate was distilled off under reduced pressure. To the residue, dichloromethane and a saturated aqueous solution of potassium carbonate were added and the organic layer was collected, followed by drying over anhydrous potassium carbonate. The solvent was distilled off under reduced pressure. The residue was dissolved in dichloromethane (350 ml), followed by the addition of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (46.5 g) under ice cooling. The reaction mixture was heated gradually to room temperature, at which stirring was conducted for 14 hours. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine (5.82 g, 10%) was obtained.

In the same manner as in Referential Example 3, a reaction was conducted using the resulting product and 4-(4-

pyridyl)benzoic acid hydrochloride as raw materials, whereby the title compound was obtained.

[0488]

^{1}H-NMR ($CDCl_3$)δ: 1.2-1.4(3H,m), 1.46(9H,s), 2.7-5.4(7H,m), 7.51(2H,d,J=5.2Hz), 7.59(2H,d,J=7.6Hz), 7.69(2H,d,J=7.6Hz), 8.69(2H,d,J=5.2Hz).

MS (FAB) m/z: 440 $(M+H)^+$.

[0489]

[Referential Example 6]

6-(4-Pyridyl)nicotinic acid hydrochloride

In tetrahydrofuran (20 ml), 6-chloronicotinic acid (535 mg) and diethyl (4-pyridyl)borane (Chem. Pharm. Bull., **33**, 4755(1985)) (500 mg) were dissolved. To the resulting solution, tetrabutylammonium bromide (546 mg), potassium hydrochloride (570 mg), tetrakis(triphenylphosphine) palladium (O) (392 mg) and water (0.5 ml) were added under an argon atmosphere, followed by heating under reflux for 6 hours. Dilute hydrochloric acid was added to the reaction mixture to make it acidic. Water and ethyl acetate were poured into the resulting mixture for extraction. The water layer so extracted was distilled off under reduced pressure. The residue was purified by a synthetic adsorbent chromatography ("Diaion HP-20" (trade name), water ~ 50% acetonitrile - water). To the resulting fraction, dilute hydrochloric acid was added to make it acidic. The solvent was then distilled off. Tetrahydrofuran was added to the residue

and the precipitate was collected by filtration, whereby the title compound (269 mg, 32%) was obtained.

[0490]

^{1}H-NMR (DMSO-d_6) δ: 8.45-8.55(2H,m), 8.65(2H,d,J=6.8Hz), 9.03(2H,d,J=6.8Hz), 9.27(1H,s).

MS (FAB) m/z: 201 $(M+H)^+$

[0491]

[Referential Example 7]

Methyl 4-(3-pyridyl)benzoate

In tetrahydrofuran (100 ml), methyl 4-bromobenzoate (5.04 g) and diethyl-3-pyridylborane (Chem. Pharm. Bull., **33**, 4755(1985)) (2.30 g) were dissolved, followed by the addition of tetrabutylammonium bromide (2.51 g), potassium hydroxide (2.63 g), tetrakis(triphenylphosphine)palladium (O) (1.8 g) and water (1 ml) under an argon atmosphere. The resulting mixture was heated under reflux for 2 hours. After ice cooling, an aqueous ammonium chloride solution and ethyl acetate were added to the reaction mixture. The organic layer collected by separation was dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (hexane: ethyl acetate = 1:1). The solvent was then distilled off. To the residue, methanol and ethanolic 1N hydrochloric acid were added. The solvent was distilled off again. Tetrahydrofuran was added to the residue and the solid so precipitated was collected by filtration. After drying, the title compound (1.76 g, 45%) was

obtained as a colorless solid.

[0492]

^{1}H-NMR (DMSO-d_6) δ: 3.91(3H,s), 8.0-8.1(3H,m), 8.1-8.15(2H,m), 8.75-8.85(1H,m), 8.85-8.95(1H,m), 9.25-9.3(1H,m).

[0493]

[Referential Example 8]

4-(3-Pyridyl)benzoic acid hydrochloride

At room temperature, methyl 4-(3-pyridyl)benzoate (1.76 g) was dissolved in a mixed solvent of 1N hydrochloric acid (50 ml) and dioxane (50 ml), followed by heating under reflux for 4 hours. The solvent was then distilled off under reduced pressure. Tetrahydrofuran was added to the residue, followed by washing, whereby the title compound (1.55 g, 93%) was obtained as a colorless solid.

[0494]

^{1}H-NMR (DMSO-d_6) δ: 7.95-8.0(3H,m), 8.10(2H,d,J=8.3Hz), 8.65-8.75(1H,m), 8.8-8.9(1H,m), 9.22(1H,d,J=2.0Hz)

[0495]

[Referential Example 9] Methyl 4-(2-aminopyridin-5-yl)benzoate

In the same manner as in Example 2, a reaction was conducted using 5-bromo-2-aminopyridine and 4-carboxyphenyboronic acid as raw materials, whereby 4-(2-aminopyridin-5-yl)benzoic acid was obtained.

The resulting 4-(2-aminopyridin-5-yl)benzoic acid (684

mg) was dissolved in methanol (50 ml) at room temperature, followed by the addition of concentrated sulfuric acid (1 ml). After heating under reflux for 2 hours, the reaction mixture was made weakly alkaline with an aqueous solution of sodium bicarbonate. Water and ethyl acetate were added to the resulting mixture and the organic layer was collected. The organic layer was then dried over anhydrous magnesium sulfate. The solvent was distilled off. Hexane was added to the residue for crystallization, whereby the title compound (243 mg, 23%) was obtained.

[0496]

^{1}H-NMR ($CDCl_3$) δ: 3.94(3H,s), 4.57(2H,br s), 6.60(1H,d,J=8.8Hz), 7.58(2H,d,J=8.8Hz), 7.72(1H,dd,J=8.8,2.4Hz), 8.09(2H,d,J=8.8Hz), 8.38(1H,d,J=2.4Hz).

MS (FAB) m/z: 229 $(M+H)^+$.

Elementary analysis for $C_{13}H_{12}N_2O_2$

Calculated: C, 68.41; H, 5.30, N, 12.27.

Found: C, 68.78; H, 5.45; N, 12.09.

[0497]

[Referential Example 10]

Methyl 4-[2-(tert-Butoxycarbonylamino)pyridin-5-yl]benzoate

At room temperature, methyl 4-(2-aminopyridin-5-yl)benzoate (200 mg) was suspended in tert-butanol (20 ml). To the resulting suspension, di-tert-butyl dicarbonate (286 mg) was added and the resulting mixture was stirred for 24 hours. After the solvent was distilled off, the residue was purified

by chromatography on a silica gel column (1% methanol - dichloromethane), whereby the title compound (155 mg, 54%) was obtained as a colorless solid.

[0498]

^{1}H-NMR ($CDCl_3$) δ: 1.55(9H,s), 3.95(3H,s), 7.63(2H,d,J=8.3Hz), 7.92(1H,dd,J=8.8,2.4Hz), 8.07(1H,d,J=8.8Hz), 8.09(1H,br s), 8.12(2H,d,J=8.3Hz), 8.55(1H,d,J=2.4Hz).

MS(FAB) m/z: 329 $(M+H)^+$.

Elementary analysis for $C_{18}H_{20}N_2O_4$

Calculated: C, 65.84; H, 6.14, N, 8.53;

Found: C, 65.67; H, 6.02; N, 8.40.

[0499]

[Referential Example 11]

4-[2-(tert-Butoxycarbonylamino)pyridin-5-yl]benzoic acid

At room temperature, methyl 4-[2-(tert-butoxycarbonylamino)pyridin-5-yl]benzoate (250 mg) was suspended in a mixed solvent of tetrahydrofuran (10 ml) and methanol (10 ml), followed by the addition of a 1N aqueous sodium hydroxide solution (8 ml). The resulting mixture was stirred for 5 hours. The reaction mixture was made weakly acidic with an aqueous citric acid solution, followed by the addition of saturated saline and n-butanol and the organic layer was collected. The resulting organic layer was then dried over anhydrous magnesium sulfate. The solvent was distilled off, whereby the title compound (120 mg, 49%) was obtained as a crude purified product.

[0500]

^{1}H-NMR (DMSO-d_6) δ: 1.49(9H,s), 7.83(2H,d,J=8.3Hz), 7.91(1H,d,J=8.8Hz), 8.02(2H,d,J=8.3Hz), 8.13(1H,dd,J=8.8,2.4Hz), 8.65(1H,d,J=2.4Hz), 9.95(1H,s), 12.99(1H,br s).

[0501]

[Referential Example 12]

1-[4-[2-(tert-Butoxycarbonylamino)pyridin-5-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a mixed solvent of dichloromethane (20 ml) and N,N-dimethylformamide (1 ml), 4-[2-(tert-butoxycarbonyl)amino]pyridin-5-yl]benzoic acid (74 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (110 mg) were suspended. To the resulting suspension, 1-hydroxybenzotriazole (35 mg) and N-methylmorpholine (34 μl) were added, followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (68 mg) under ice cooling. After stirring at room temperature for 6 hours, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (1% methanol - dichloromethane). The solvent was then distilled off, whereby the title compound (128 mg, 90%) was obtained.

[0502]

^{1}H-NMR ($CDCl_3$) δ: 1.54(9H,s), 3.00-3.30(4H,m), 3.50-4.10(4H,m),

7.39(2H,d,J=7.8Hz), 7.54(2H,d,J=7.8Hz), 7.60(1H,dd,J=8,8,2.0Hz), 7.71(1H,dd,J=8.8,1.5Hz), 7.84(1H,dd,J=8.8,2.4Hz), 7.88(1H,br s), 7.9-8.0(3H,m), 8.03(1H,d,J=8.8Hz), 8.31(1H,s), 8.46(1H,d,J=2.4Hz).

[0503]

[Referential Example 13]

4-(4-Aminophenyl)benzoic acid hydrochloride

In the same manner as in Referential Example 2, a reaction was conducted using 4-bromoaniline and 4-carboxyphenylboronic acid as raw materials, whereby the title compound was obtained.

[0504]

^{1}H-NMR (DMSO-d_6) δ: 7.31(2H,d,J=7.3Hz), 7.75-7.85(4H,m), 8.09(2H,d,J=8.3Hz).

MS (FAB) m/z: 228 $(M+H)^+$.

Elementary analysis for $C_{13}H_{11}NO_2 \cdot HCl$

Calculated: C, 62.53; H, 4.84, N, 5.61; Cl, 14.20.

Found: C, 62.33; H, 4.83; N, 5.50; Cl, 14.14.

[0505]

[Referential Example 14]

Methyl 4-[4-(tert-butoxycarbonylamino)phenyl]benzoate

In the same manner as in Referential Example 9 or 10, a reaction was conducted using 4-(4-aminophenyl)benzoic acid hydrochloride as a raw material, whereby the title compound was obtained.

[0506]

^{1}H-NMR ($CDCl_3$) δ: 1.54(9H,s), 3,94(3H,s), 6.56(1H,br s), 7.46(2H,d,J=8.8Hz), 7.57(2H,d,J=8.8Hz), 7.63(2H,d,J=8.3Hz), 8.08(2H,d,J=8.3Hz).

MS (FAB)m/z: 328 $(M+H)^+$.

Elementary analysis for $C_{19}H_{21}NO_4$

Calculated: C, 69.71; H, 6.47, N, 4.28.

Found: C, 69.49; H, 6.44; N, 4.42.

[0507]

[Referential Example 15]

4-[4-(tert-Butoxycarbonylamino)phenyl]benzoic acid

In the same manner as in Referential Example 11, a reaction was conducted using methyl 4-[4-(tert-butoxycarbonylamino)phenylbenzoate as a raw material, whereby the title compound was obtained.

[0508]

^{1}H-NMR ($CDCl_3$) δ: 1.54(9H,s), 6.57(1H,br s), 7.47(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 7.66(2H,d,J=8.3Hz), 8.13(2H,d,J=8.3Hz).

MS (FAB) m/z: 314 $(M+H)^+$.

Elementary analysis for $C_{18}H_{19}NO_4$

Calculated: C, 68.99; H, 6.11, N, 4.47.

Found: C, 68.91; H, 6.27; N, 4.24.

[0509]

[Referential Example 16]

1-[4-[4-(tert-Butoxycarbonylamino)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-[4-(tert-butoxycarbonylamino)phenyl]benzoic acid (150 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (203 mg) as raw materials, whereby the title compound (303 mg, 100%) was obtained.

[0510]

^{1}H-NMR ($CDCl_3$) δ: 1.53(9H,s), 2.90-3.30(4H,m), 3.50-4.10(4H,m), 6.56(1H,s), 7.35(2H,d,J=8.3Hz), 7.44(2H,d,J=8.3Hz), 7.49(2H,d,J=8.3Hz), 7.54(2H,d,J=8.3Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.90-7.95(3H,m), 8.30(1H,br s).

[0511]

[Referential Example 17]

Methyl 4-acetylbenzoate

In a mixed solvent of tetrahydrofuran (100 ml) and methanol (7 ml), methyl 4-acetylbenzoate (3.28 g) was dissolved at room temperature, followed by the addition of trimethylsilyldiazomethane (a 2.0M hexane solution, 12 ml) in portions under ice cooling. After heating to room temperature and stirring for 30 minutes, the solvent was distilled off. To the residue, an aqueous solution of sodium bicarbonate and ether were added. The organic layer collected by separation was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was crystallized from hexane, whereby the title compound (2.90 g, 82%) was obtained.

[0512]

^{1}H-NMR ($CDCl_3$) δ: 2.65(3H,s), 3.96(3H,s), 8.01(2H,d,J=8.3Hz), 8.13(2H,d,J=8.3Hz).

MS (EI) m/z: $178M^{+}$.

Elementary analysis for $C_{10}H_{10}O_3$

Calculated: C, 67.41; H, 5.66.

Found: C, 67.28; H, 5.53.

[0513]

[Referential Example 18]

Methyl 4-bromoacetylbenzoate

At 15°C, methyl 4-acetylbenzoate (2.23 g) was dissolved in a hydrobromic acid acetic acid solution (30%, 10 ml). Bromine was gradually added dropwise to the reaction mixture to maintain its temperature at 15°C. After stirring for 10 minutes, the reaction mixture was cooled to 4°C. A mixed solvent of methanol (50 ml) and water (50 ml) was added to the reaction mixture for crystallization, followed by washing with hexane. By the collection through filtration, the title compound (2.29 g, 71%) was obtained as a colorless solid.

[0514]

^{1}H-NMR ($CDCl_3$) δ: 3.96(3H,s), 4,47(2H,s), 8.05(2H,d,J=8.8Hz), 8.16(2H,d,J=8.8Hz).

MS (FAB) m/z: 257 [$(M+H)^{+}$, ^{79}Br], 259 [$(M+H)^{+}$, ^{81}Br].

Elementary analysis for $C_{10}H_9BrO_3$

Calculated: C, 46.72; H, 3.53.

Found: C, 46.36; H, 3.63.

[0515]

[Referential Example 19]

Methyl 4-(2-aminothiazol-4-yl)benzoate

At room temperature, methyl 4-bromoacetylbenzoate (1.00 g) and thiourea (296 mg) were dissolved in isopropanol (100 ml), followed by heating under reflux for 15 minutes. Under stirring at the same temperature, anhydrous sodium carbonate (206 mg) was added to the reaction mixture. The resulting mixture was heated under reflux for 20 minutes. After completion of the reaction, water (50 ml) was added under ice cooling and the solid so precipitated was collected by filtration. The solid was dissolved in water and dichloromethane. The organic layer collected by separation was dried over anhydrous sodium sulfate. The solvent was then distilled off. The pale yellow solid so precipitated was washed with ether, whereby the title compound (634 mg, 70%) was obtained.

[0516]

^{1}H-NMR ($CDCl_3$) δ: 3.93(3H,s), 4.96(2H,br s), 6.88(1H,s), 7.85(2H,d,J=8.8Hz), 8.05(2H,d,J=8.8Hz).

MS (FAB) m/z: 235 $(M+H)^+$.

[0517]

[Referential Example 20]

4-(2-Aminothiazol-4-yl)benzoic acid

At room temperature, methyl 4-(2-aminothiazol-4-yl)benzoate (300 mg) was suspended in a mixed solvent of

tetrahydrofuran (5 ml) and methanol (5 ml), followed by the addition of a 1N aqueous sodium hydroxide solution (10 ml). The resulting mixture was stirred for one hour. To the reaction mixture, N,N-dimethylformamide (5 ml) was added, followed by heating under reflux for 6 hours. After completion of the reaction, the solvent was distilled off. To the residue, water and 1N hydrochloric acid were added successively and the pale yellow solid so precipitated was collected by filtration, whereby the title compound (229 mg, 69%) was obtained as a pale yellow solid.

[0518]

^{1}H-NMR (DMSO-d_6) δ: 7.30(1H,br s), 7.87(2H,d,J=8.3Hz), 7.95-8.00(2H,m).

MS (FAB) m/z: 221 $(M+H)^+$.

Elementary analysis for $C_{10}H_8N_2O_2S\cdot 0.75HCl\cdot 0.6H_2O$

Calculated: C, 46.48; H, 3.88, N, 10.84; Cl, 10.29; S, 12.41.

Found: C, 46.36; H, 4.12, N, 10.64; Cl, 10.05; S, 12.33.

[0519]

[Referential Example 21]

Methyl 4-(imidazol-4-yl)benzoate

At room temperature, methyl 4-bromoacetylbenzoate (2 g) was dissolved in formamide (100 ml), followed by stirring at 180°C for 90 minutes. After completion of the reaction, the reaction mixture was ice cooled and dissolved in water and 1N hydrochloric acid. The resulting solution was purified by a synthetic adsorbent chromatography ("Diaion HP-20" (trade

name), water ~ 50% acetonitrile - water). The crude product so obtained was purified further by chromatography on a silica gel column (5% methanol - dichloromethane), whereby the title compound (844 mg, 54%) was obtained as a pale yellow solid.

[0520]

^{1}H-NMR ($CDCl_3$) δ: 3.93(3H,s), 7.46(1H,s), 7.75(1H,s), 7.86(2H,m), 8.07(2H,d,J=8.3Hz).

MS (FAB) m/z: 203 $(M+H)^+$.

[0521]

[Referential Example 22]

Methyl 4-[1-triphenylmethylimidazol-4(5)-yl]benzoate

Methyl 4-(imidazol-4-yl)benzoate (828 mg) was dissolved in dichloromethane (50 ml), followed by the addition of diisopropylethylamine (856 μl) and triphenylmethyl chloride (1.37 g) under ice cooling. The resulting mixture was stirred at room temperature for 16 hours. The solvent was distilled off. The residue was purified by chromatography on a silica gel column (dichloromethane), whereby the title compound (1.08 g, 59%) was obtained as a colorless glassy solid.

[0522]

^{1}H-NMR ($CDCl_3$) δ: 3.90(3H,s), 7.15-7.22(6H,m), 7.23(1H,d,J=1.5Hz), 7.30-7.40(15H,m), 7.52(1H,d,J=1.5Hz), 7.79(2H,d,J=8.3Hz), 8.01(2H,d,J=8.3Hz).

MS (FAB) m/z: 445 $(M+H)^+$.

[0523]

[Referential Example 23]

4-[1-Triphenylmethylimidazol-4(5)-yl]benzoic acid

At room temperature, methyl 4-[1-triphenylmethylimidazol-4(5)-yl]benzoate (1.04 g) was dissolved in a mixed solvent of tetrahydrofuran (10 ml) and methanol (10 ml). To the resulting solution, a 3N aqueous sodium hydroxide solution (6 ml) was added, followed by stirring for 5 hours. Tetrahydrofuran and methanol were removed from the reaction mixture by distillation under reduced pressure. An aqueous citric acid solution was added to the residue to make it weakly acidic, followed by the addition of water and dichloromethane. The organic layer collected by separation was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was distilled off, whereby the title compound (1.13 g, quant.) was obtained as a crude purified product in the form of a colorless glassy solid.

[0524]

^{1}H-NMR ($CDCl_3$) δ: 7.15-7.22(6H,m), 7.23(1H,d,J=1.5Hz), 7.30-7.40(9H,m), 7.69(1H,d,J=1.5Hz), 7.81(2H,d,J=8.3Hz), 8.10(2H,d,J=8.3Hz).

[0525]

[Referential Example 24]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[1-triphenylmethylimidazol-4(5)-yl)]benzoyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-[1-triphenylmethylimidazol-4(5)-

yl]benzoic acid (371 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (300 mg) as raw materials, whereby the title compound (560 mg, 90%) was obtained in the form of a colorless glassy solid.

[0526]

^{1}H-NMR ($CDCl_3$) δ: 2.90-3.30(4H,m), 3.50-4.10(4H,m), 7.15-7.20(6H,m), 7.28(2H,d,J=8.3Hz), 7.30-7.40(9H,m), 7.49(1H,d,J=1.0Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.71(2H,d,J=8.3Hz), 7.75(1H,dd,J=8.8,1.5Hz), 7.90-7.95(3H,m), 8.29(1H,br s).

MS (FAB) m/z: 723 $(M+H)^+$.

[0527]

[Referential Example 25]

4-[2-Aminoimidazol-4-yl]benzoic acid hydrochloride

At room temperature, methyl 4-bromoacetylbenzoate (1.37 g) and acetylguanidine (1.62 g) were suspended in acetonitrile, followed by heating under reflux for 16 hours. The solvent was then distilled off under reduced pressure. Water was added to the residue. The insoluble matter so precipitated was collected by filtration, followed by washing with ethanol, whereby methyl 4-[2-aminoimidazol-4-yl]benzoate was obtained. The resulting product was dissolved in a mixed solvent of dioxane (10 ml) and 1N hydrochloric acid (10 ml), followed by heating under reflux for 8 hours. The residue obtained by distilling off the solvent was solidified by tetrahydrofuran and then collected by filtration, whereby the title compound (500 mg,

39%) was obtained.

[0528]

^{1}H-NMR (DMSO-d_6) δ: 7.55-7.65(3H,m), 7.80(2H,d,J=8.3Hz), 7.98(2H,d,J=8.3Hz), 12.2-13.3(3H,m).

MS (FAB) m/z: 204 $(M+H)^+$.

Elementary analysis for $C_{10}H_9N_3O_2 \cdot HCl \cdot 0.5H_2O$

Calculated: C, 48.30; H, 4.46; N, 16.90; Cl, 14.26.

Found: C, 48.03; H, 4.10; N, 16.49; Cl, 14.12.

[0529]

[Referential Example 26]

1-[4-Bromo-2-(tert-butoxycarbonyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (200 ml), 4-bromophthalic anhydride (1.96 g) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (3.00 g) were suspended under ice cooling. To the resulting suspension, diisopropylethylamine (3.76 ml) was added, followed by stirring for 20 minutes. To the reaction mixture, dilute hydrochloric acid and dichloromethane were added. The organic layer collected by separation was dried over anhydrous sodium sulfate. The solvent was concentrated so that the volume was reduced to 200 ml. To the concentrate, N,N'-diisopropyl-O-tert-butylisourea (2.6 g) was added under ice cooling and the resulting mixture was stirred at room temperature for 3 days. Dilute hydrochloric acid and dichloromethane were added to the reaction mixture. The organic layer collected by separation was dried over anhydrous

sodium sulfate. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 ~ 1:1), whereby the title compound (1.78 g, 35%) was obtained as a colorless solid.

[0530]

^{1}H-NMR ($CDCl_3$) δ: 1.30(9H,s), 2.90-3.40(6H,m), 3.80-4.00(2H,m), 7.01(1H,d,J=8.3Hz), 7.59(1H,dd,J=8.3,2.0Hz), 7.61(1H,dd,J=8.3,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.85-7.95(3H,m), 8.00(1H,d,J=2.0Hz), 8.29(1H,br s).

[0531]

[Referential Example 27]

1-[2-tert-Butoxycarbonyl-4-(pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Referential Example 7, a reaction was conducted using 1-[4-bromo-2-(tert-butoxycarbonyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine and diethyl(4-pyridyl)borane (Chem. Pharm. Bull., 33, 4755(1985)) as raw materials, whereby the title compound was obtained.

[0532]

^{1}H-NMR ($CDCl_3$) δ: 1.37(9H,s), 2.80-3.50(6H,m), 3.80-4.00(2H,m), 7.40(1H,d,J=7.8Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.77(1H,dd,J=8.3,1.5Hz), 7.87(1H,dd,J=7.8,2.0Hz), 7.90-7.95(3H,m), 8.10(2H,d,J=6.8Hz), 8.25(1H,d,J=2.0Hz), 8.31(1H,br s), 8.90(2H,d,J=6.8Hz).

MS (FAB) m/z: 592 $(M+H)^+$.

Elementary analysis for $C_{31}H_{30}ClN_3O_5S \cdot HCl \cdot 0.2H_2O \cdot THF$

Calculated: C, 59.69; H, 5.64; N, 5.97; Cl, 10.07; S, 4.55.

Found: C, 59.55; H, 5.45; N, 5.87; Cl, 9.97; S, 4.68.

[0533]

[Referential Example 28]

5-(4-Pyridyl)thiophene-2-carboxylic acid hydrochloride

In the same manner as in Referential Example 6, a reaction was conducted using 5-bromothiophene-2-carboxylic acid and diethyl (4-pyridyl)borane (Chem. Pharm. Bull., 33, 4755(1985)) as raw materials, whereby the title compound was obtained.

[0534]

^{1}H-NMR (DMSO-d_6) δ: 7.87(1H,d,J=3.9Hz), 8.17(1H,d,J=3.9Hz), 8.29(2H,d,J=6.8Hz), 8.88(2H,d,J=6.8Hz).

MS (FAB) m/z: 206 $(M+H)^+$.

Elementary analysis for $C_{10}H_7NO_2S \cdot HCl \cdot 0.8H_2O$

Calculated: C, 46.90; H, 3.78; N, 5.47; Cl, 13.84; S, 12.52.

Found: C, 46.77; H, 3.76; N, 5.27; Cl, 13.83; S, 12.56.

[0535]

[Referential Example 29]

5-(4-Pyridyl)furan-2-carboxylic acid hydrochloride

In the same manner as in Referential Example 6, a reaction was conducted using 5-bromofuran-2-carboxylic acid and diethyl (4-pyridyl)borane (Chem. Pharm. Bull., 33, 4755(1985)) as raw materials, whereby the title compound was obtained.

[0536]

^{1}H-NMR (DMSO-d_6) δ: 7.49(1H,d,J=3.4Hz), 7.80-7.90(1H,m), 8.20-8.30(2H,m), 8.85-8.95(2H,m).

[0537]

[Referential Example 30]

4-(2-Pyridyl)benzoic acid hydrochloride

To water (200 ml), 2-(p-tolyl)pyridine (17.2 g) was added. To the resulting mixture, potassium permanganate (21.0 g) was added, followed by heating under reflux for 18 hours. After the precipitate was filtered off, dichloromethane was added to the filtrate to collect the water layer. The water layer was then made acidic with 2N hydrochloric acid. The acidic aqueous solution was concentrated. The precipitate was collected by filtration, followed by washing with water and ethyl acetate, whereby the title compound (7.07 g, 35%) was obtained as a white solid.

[0538]

^{1}H-NMR (DMSO-d_6) δ: 7.60(1H,t,J=5.9Hz), 8.08(2H,d,J=7.8Hz), 8.17(2H,m), 8.21(2H,d,J=7.8Hz), 8.78(1H,d,J=4.9Hz).

MS (EI) m/z: 199M^+.

[0539]

[Referential Example 31]

1-[(E)-4-Chlorostyrylsulfonyl)piperazine hydrochloride

In the same manner as in Referential Example 1, a reaction was conducted using tert-butyl 1-piperazinecarboxylate and

(E)-4-chlorostyrylsulfonyl chloride (WO96/10022) as raw materials, whereby the title compound was obtained.

[0540]

^{1}H-NMR (DMSO-d_6) δ: 3.20(4H,br s), 3.33-3.38(4H,m), 7.47(2H,s), 7.53(1H,d,J=8.8Hz), 7.82(1H,d,J=8.8Hz).

Elementary analysis for $C_{12}H_{15}ClN_2O_2S \cdot HCl$

Calculated: C, 44.59; H, 4.99, Cl, 21.94; N, 8.67; S, 9.92.

Found: C, 44.42; H, 4.78, Cl, 21.83; N, 8.68; S, 9.87.

[0541]

[Referential Example 32]

4-(2,4-Diamino-6-pyrimidyl)benzoic acid hydrochloride

In toluene (9 ml), 6-chloro-2,4-diaminopyrimidine (434 mg) was dissolved, followed by the addition of 4-carboxyphenylboronic acid (667 mg), ethanol (2.5 ml), sodium carbonate (635 mg), water (3.0 ml) and bis(triphenylphosphine)palladium (II) dichloride (65 mg). The resulting mixture was heated under reflux for 24 hours under an argon gas atmosphere. Ethyl acetate and water were added to the reaction mixture. The water layer so separated was made acidic with 2N hydrochloric acid. The insoluble matter was collected by filtration, washed with water and tetrahydrofuran and then dried, whereby the title compound (371 mg, 54%) was obtained.

[0542]

^{1}H-NMR (DMSO-d_6) δ: 6.43(1H,s), 7.30-7.80(2H,br),

7.96(2H,d,J=7.8Hz), 8.12(2H,d,J=7.8Hz), 8.27(2H,br s), 12.77(1H,br), 13.33(1H,br).

MS (EI) m/z: 230M$^+$.

Elementary analysis for $C_{11}H_{10}N_4O_2S \cdot 0.95HCl \cdot 1.9H_2O$

Calculated: C, 44.17; H, 4.97; Cl, 11.26; N, 18.73.

Found: C, 44.33; H, 4.97; Cl, 11.32; N, 18.65.

[0543]

[Referential Example 33]

1-tert-Butoxycarbonyl-4-[4-(2-pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 3, a reaction was conducted using 4-(2-pyridyl)benzoic acid hydrochloride obtained in Referential Example 30 and tert-butyl 1-piperazinecarboxylate as raw materials, whereby the title compound was obtained.

[0544]

^{1}H-NMR ($CDCl_3$)δ: 1.47(9H,s), 3.43(4H,br), 3.51(2H,br), 3.76(2H,br), 7.28(1H,d,J=5.9Hz), 7.52(2H,d,J=7.8Hz), 7.76(1H,m), 7.79(1H,m), 8.05(2H,d,J=7.8Hz), 8.71(1H,d,J=4.9).

MS (FAB) m/z: 368 (M+H)$^+$.

Elementary analysis for $C_{21}H_{25}N_3O_3 \cdot 0.1H_2O$

Calculated: C, 68.31; H, 6.88; N, 11.38;

Found: C, 68.26; H, 6.86; N, 11.42.

[0545]

[Referential Example 34]

2-[4-[[4-(tert-Butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

At -10°C, metachloroperbenzoic acid (789 mg) was added to a solution of 1-tert-butoxycarbonyl-4-[4-(2-pyridyl)benzoyl]piperazine (517 mg) in dichloromethane (dichloromethane: 8 ml). The resulting mixture was stirred for 24 hours, followed by dilution with dichloromethane. A small amount of an aqueous sodium thiosulfate solution and saturated saline were added and the organic layer was collected. The resulting organic layer was washed with a saturated aqueous solution of sodium bicarbonate and saturated saline and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 20:1), whereby the title compound (415 mg, 77%) was obtained.

[0546]

^{1}H-NMR ($CDCl_3$)δ: 1.48(9H,s), 3.47(6H,br), 3.76(2H,br), 7.29(1H,m), 7.34(1H,t,J=7.8Hz), 7.44(1H,dd,J=7.8,2.0Hz), 7.52(2H,d,J=7.8Hz), 7.90(2H,d,J=7.8Hz), 8.35(1H,d,J=5.9Hz).

MS (FAB) m/z: 384 $(M+H)^+$.

[0547]

[Referential Example 35]

2-[4-[(1-Piperazinyl)carbonyl]phenyl]pyridine N-oxide

In dichloromethane (2.5 ml), 2-[4-[[4-(tert-butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-

oxide was dissolved. To the resulting solution, a saturated solution of ethanol hydrochloride (2.5 ml) was added, followed by stirring at room temperature for 1 hour. After the solvent was distilled off under reduced pressure, water was added to the residue, whereby an aqueous solution was obtained. Acetone was added to the aqueous solution until the solution became turbid. The precipitate was collected by filtration and washed with acetone, whereby the title compound (274 mg, 81%) was obtained.

[0548]

^{1}H-NMR (DMSO-d_6) δ: 3.17(4H,br s), 3.50-3.95(4H,br), 7.43(1H,d,J=3.9Hz), 7.44(1H,d,J=3.9Hz), 7.57(2H,d,J=8.8Hz), 7.66(1H,t,J=3.9Hz), 7.92(2H,d,J=8.8Hz), 8.36(1H,t,J=3.9Hz), 9.21(2H,br).

MS (FAB) m/z: 284 $(M+H)^+$.

[0549]

[Referential Example 36]

1-(tert-Butoxycarbonyl)-4-[4-(3-pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 3, a reaction was conducted using 4-(3-pyridyl)benzoic acid hydrochloride obtained in Referential Example 8 and tert-butyl 1-piperazinecarboxylate as raw materials, whereby the title compound was obtained.

[0550]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.35-3.85(8H,br),

7.38(1H,dd,J=7.8,4.9Hz), 7.52(2H,d,J=8.3Hz), 7.63(2H,d,J=8.3Hz), 7.88(1H,m), 8.62(1H,dd,J=1.5,4.9Hz), 8.84(1H,d,J=2.0Hz).

[0551]

[Referential Example 37]

3-[4-[[4-(tert-Butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Referential Example 34, the title compound was obtained as a colorless solid by using 1-(tert-butoxycarbonyl)-4-[4-(3-pyridyl)benzoyl]piperazine as a raw material.

[0552]

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 3.35-4.83(8H,br), 7.38(1H,m), 7.47(1H,m), 7.49-7.65(4H,m), 8.23(1H,dd,J=6.4,1.5Hz), 8.47(1H,t,J=1.5Hz).

MS (FAB) m/z: 384 $(M+H)^+$.

Elementary analysis for $C_{21}H_{25}N_3O_4 \cdot 0.25H_2O$

Calculated: C, 65.02; H, 6.63; N, 10.83.

Found: C, 65.30; H, 6.65; N, 10.43.

[0553]

[Referential Example 38]

2-Hydroxy-4-(4-pyridyl)benzoic acid

In water (22.5 ml) and a 47% aqueous solution of hydrobromic acid (22.5 ml), 4-amino-2-hydroxybenzoic acid (5.04 g) was dissolved. While the resulting solution was maintained at 5°C or lower, an aqueous solution (water: 15.0 ml) of sodium nitrite

(2.26 g) was added dropwise thereto, followed by stirring for 30 minutes under ice cooling. The reaction mixture was added, in portions, to a solution of cuprous bromide (5.63 g) dissolved in a 47% aqueous solution of hydrobromic acid (15 ml) under ice cooling. The resulting mixture was stirred at room temperature for 150 minutes. Ethyl acetate was added to the reaction mixture for extraction. The organic layer so obtained was washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 10% methanol - dichloromethane), whereby 4-bromo-2-hydroxybenzoic acid (5.51 g) was obtained as a crudely purified product.

The crudely purified product (298 mg) was reacted as in Referential Example 6, whereby the title compound (70 mg, 21%) was obtained.

[0554]

^{1}H-NMR (DMSO-d_6) δ: 7.30-7.40(2H,m), 7.78(2H,d,J=4.4Hz), 7.92(1H,d,J=6.3Hz), 8.69(2H,d,J=5.9Hz).

MS (FAB) m/z: 216 $(M+H)^+$.

[0555]

[Referential Example 39]

4-Bromo-3-hydroxybenzoic acid

In acetic acid (24.5 ml), 3-hydroxybenzoic acid (5.00 g) was suspended. To the resulting suspension, a solution of

bromine (1.9 ml) in acetic acid (acetic acid: 5 ml) was added dropwise under ice cooling, followed by stirring at room temperature for 33 hours. The reaction mixture was ice cooled. The crystals so precipitated were collected by filtration and then washed with acetic acid, whereby the title compound (1.68 g, 21%) was obtained.

[0556]

^{1}H-NMR (DMSO-d_6) δ: 7.28(1H,dd,J=7.8,2.0Hz), 7.51(1H,d,J=2.0Hz), 7.59(1H,d,J=8.3Hz), 10.54(1H,br s), 12.84(1H,br).

[0557]

[Referential Example 40]

Methyl 4-bromo-3-methoxybenzoate

In the same manner as in Referential Example 17, a reaction was conducted using 4-bromo-3-hydroxybenzoic acid as a raw material, whereby the title compound was obtained.

[0558]

^{1}H-NMR ($CDCl_3$) δ: 3.92(3H,s), 3.96(3H,s), 7.51(1H,dd,J=8.3,2.0Hz), 7.55(1H,d,J=2.0Hz), 7.61(1H,d,J=8.8Hz).

[0559]

[Referential Example 41]

3-Methoxy-4-(4-pyridyl)benzoic acid

In the same manner as in Referential Example 7, a reaction was conducted using methyl 4-bromo-3-methoxybenzoate and

diethyl (4-pyridyl)borane (Chem. Pharm. Bull., 33, 4755(1985)). The crude product so obtained was reacted as in Referential Example 8, whereby the title compound was obtained.

[0560]

^{1}H-NMR ($CDCl_3$)δ: 3.93(3H,s), 7.65-7.75(3H,m), 8.20(2H,d,J=5.4Hz), 8.94(2H,d,J=6.3Hz).

MS (FAB) m/z: 230 $(M+H)^+$.

[0561]

[Referential Example 42]

4-tert-Butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In dichloromethane (18 ml), 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine (517 mg) and 6-chloro-2-naphthylsulfonyl chloride (WO96/10022) (588 mg) were dissolved under ice cooling. To the resulting solution, diisopropylethylamine (0.59 ml) was added, followed by stirring at room temperature for 63 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (688 mg, 71%) was obtained.

[0562]

^{1}H-NMR ($CDCl_3$)δ: 1.05(3H,t,J=7.1Hz), 1.38(9H,s), 2.80-4.70(9H,m), 7.55(1H,dd,J=8.6,2.2Hz), 7.77(1H,dd,J=8.6,1.7Hz), 7.85-7.90(3H,m), 8.33(1H,s).

MS (FAB) m/z: 483[$(M+H)^+$, Cl^{35}], 485[$(M+H)^+$, Cl^{37}].

[0563]

[Referential Example 43]

4-tert-Butoxycarbonyl-2-ethoxycarbonyl-1-[4-(3-pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(3-pyridyl)benzoic acid and 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine as raw materials, whereby the title compound was obtained.

[0564]

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.40(3H,m), 1.46(9H,s), 2.70-4.80(8H,m), 5.35(1H,br), 7.35-7.70(5H,m), 7.85-7.95(1H,m), 8.64(2H,dd,J=4.6,1.7Hz), 8.86(1H,s).

MS (FAB) m/z: 440 $(M+H)^+$.

[0565]

[Referential Example 44]

Methyl N-tert-butoxycarbonyltranexamate

To methanol (20 ml), thionyl chloride (1 ml) was added dropwise under ice cooling, followed by the addition of tranexamic acid (2.04 g). The resulting mixture was heated under reflux for 3 hours. The residue obtained by distilling the reaction mixture under reduced pressure was pulverized in ether and then collected by filtration, whereby colorless crystals (2.31 g) were obtained.

The resulting crystals (2.10 g) were dissolved in dichloromethane (40 ml), followed by the addition of N-methylmorpholine (1.2 ml). To the resulting mixture, a

solution of di-tert-butyl dicarbonate (2.51 g) in dichloromethane (dichloromethane: 3 ml) was added under ice cooling. The resulting mixture was stirred at room temperature for 18 hours. After diluted with dichloromethane, the reaction mixture was washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 ~ 3:1), followed by recrystallization from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals (2.09 g, 65%) was obtained.

[0566]

^{1}H-NMR ($CDCl_3$) δ: 0.90-1.10(2H,m), 1.40-1.60(12H,m), 1.80-1.90(2H,m), 2.00-2.10(2H,m), 2.24(1H,m), 2.98(2H,m), 3.66(3H,s), 4.58(1H,br).

Elementary analysis for $C_{14}H_{25}NO_4$

Calculated: C, 61.97; H, 9.29; N, 5.16.

Found: C, 62.15; H, 9.42; N, 5.12.

[0567]

[Referential Example 45]

trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylmethanol

Methyl N-tert-butoxycarbonyltranexamate (1.00 g) was dissolved in a mixed solution of tetrahydrofuran (10 ml) and methanol (2 ml). To the resulting solution, sodium borohydride

(0.44 g) was added under ice cooling, followed by stirring at room temperature for 24 hours. After the addition of water, the reaction mixture was concentrated under reduced pressure. Ethyl acetate and dilute hydrochloric acid were added to the concentrate. The organic layer collected by separation was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column in repetition (first time; dichloromethane ~ dichloromethane : methanol = 20:1, second time; hexane : ethyl acetate = 3:1), whereby colorless crystals (0.74 g, 82%) were obtained. A portion of the crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

[0568]

^{1}H-NMR ($CDCl_3$)δ: 0.90-1.10(4H,m), 1.30-1.60(12H,m), 1.80-2.00(4H,m), 2.98(2H,m), 3.45(2H,d,J=6.4Hz), 4.59(1H,br).

Elementary analysis for $C_{13}H_{25}NO_3$

Calculated: C, 64.17; H, 10.35, N, 5.76.

Found: C, 64.31; H, 10.03; N, 5.74.

[0569]

[Referential Example 46]

trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexanecarboxaldehyde

In dichloromethane (5 ml), trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylmethanol (0.20 g) was

dissolved, followed by the addition of pyridinium chlorochromate (0.23 g). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (0.15 g, 76%) was obtained.

[0570]

^{1}H-NMR ($CDCl_3$) δ: 1.00(2H,m), 1.27(2H,m), 1.40-1.60(1H,m), 1.44(9H,s), 1.88(2H,m), 2.02(2H,m), 2.18(1H,m), 3.00(2H,t,J=6.4Hz), 4.61(1H,br), 9.62(1H,s).

MS (FAB) m/z: 242 $(M+H)^+$.

[0571]

[Referential Example 47]

1-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylmethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (7 ml), trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexane carboxaldehyde (0.13 g) was dissolved, followed by the addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (0.24 g), triethylamine (78 µl) and sodium triacetoxyborohydride (0.17 g). The resulting mixture was stirred at room temperature for 11 hours under an argon gas atmosphere. To the reaction mixture, an aqueous solution of sodium bicarbonate was added, followed by dilution with dichloromethane. The organic layer collected by separation was dried over anhydrous sodium sulfate. The residue obtained by

distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (0.29 g, 100%) was obtained.

[0572]

^{1}H-NMR ($CDCl_3$) δ: 0.70-0.90(4H,m), 1.30-1.50(2H,m), 1.42(9H,s), 1.70-1.80(4H,m), 2.09(2H,d,J=7.3Hz), 2.46(4H,m), 2.92(2H,m), 3.08(4H,m), 4.53(1H,br), 7.56(1H,dd,J=8.8,2.0Hz), 7.78(1H,dd,J=8.8,2.0Hz), 7.80-8.00(3H,m), 8.30(1H,s).

MS (FAB) m/z: 536[$(M+H)^+$, Cl^{35}], 538[$(M+H)^+$, Cl^{37}].

[0573]

[Referential Example 48]

1-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

A reaction was conducted as in Referential Example 11 and 12, whereby the title compound was obtained.

[0574]

^{1}H-NMR ($CDCl_3$) δ: 0.80-1.00(2H,m), 1.40-1.60(3H,m), 1.42(9H,s), 1.60-1.70(2H,m), 1.70-1.90(2H,m), 2.30(1H,m), 2.95(2H,m), 3.07(4H,m), 3.58(2H,br), 3.70(2H,br), 4.57(1H,m), 7.58(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,1.5Hz), 7.90-8.00(3H,m), 8.30(1H,s).

MS (FD) m/z: 549(M^+, Cl^{35}), 551(M^+, Cl^{37}).

[0575]

[Referential Example 49]

N-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycine benzyl ester

In the same manner as in Referential Examples 11 and 12, a reaction was conducted using methyl N-tert-butoxycarbonyltranexamate and glycine benzyl ester as raw materials, whereby the title compound was obtained.

[0576]

^{1}H-NMR ($CDCl_3$) δ: 0.96(2H,m), 1.44(9H,s), 1.40-1.60(3H,m), 1.80-1.90(2H,m), 1.90-2.00(2H,m), 2.10(1H,m), 2.98(2H,m), 4.08(2H,d,J=4.9Hz), 4.57(1H,br), 5.19(2H,s), 5.97(1H,m), 7.30-7.40(5H,m).

Elementary analysis for $C_{22}H_{32}N_2O_5$

Calculated: C, 65.32; H, 7.97; N, 6.93.

Found: C, 65.05; H, 7.89; N, 7.16.

[0577]

[Referential Example 50]

1-[N-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (11 ml), N-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycine benzyl ester (0.22 g) was suspended. To the resulting suspension, 10% palladium carbon (water content: about 50%, 50 mg) was added, followed by catalytic reduction at normal pressure and room temperature for 14 hours. After the removal of the catalyst

by filtration, the solvent was distilled off under reduced pressure. The residue so obtained was reacted as in Referential Example 12, whereby the title compound (0.32 g, 98%) was obtained.

[0578]

^{1}H-NMR ($CDCl_3$) δ: 0.80-1.00(2H,m), 1.30-1.50(3H,m), 1.43(9H,s), 1.80-2.00(4H,m), 2.06(1H,m), 2.95(2H,m), 3.10-3.20(4H,m), 3.52(2H,m), 3.74(2H,m), 3.94(2H,d,J=4.4Hz), 4.54(1H,m), 6.40(1H,m), 7,59(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.8,1.5Hz), 7.80-8.00(3H,m), 8.30(1H,s).

MS (FAB) m/z: 607 [$(M+H)^+$, Cl^{35}], 609 [$(M+H)^+$, Cl^{37}].

[0579]

[Referential Example 51]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

Homopiperazine (5 g) was dissolved in tetrahydrofuran (100 ml) at room temperature. To the resulting solution, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (12.3 g) was added in portions, followed by stirring for 3 hours. After completion of the reaction, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (10 to 20% methanol - dichloromethane), followed by the addition of ethanolic 1N hydrochloric acid. The solvent was then distilled off. The residue was solidified by the addition of ethanol, whereby powders (7.46 g) were obtained. The resulting powders were reacted as in Referential Example 1, whereby the

title compound was obtained.

[0580]

^{1}H-NMR (DMSO-d_6) δ: 2.00(2H,br s), 3.10-3.30(4H,m), 3.30-3.50(2H,m), 3.55-3.65(2H,m), 7.72(1H,d,J=8.8Hz), 7.89(1H,d,J=8.3Hz), 8.17(1H,d,J=8.8Hz), 8.22-8.28(2H,m), 8.56(1H,s), 9.29(2H,br s).

MS (FAB) m/z: 325 $(M+H)^+$.

Elementary analysis for $C_{15}H_{17}ClN_2O_2S \cdot HCl$

Calculated: C, 49.89; H, 5.02; N, 7.75; Cl, 19.63.

Found: C, 49.94; H, 5.05; N, 7.47; Cl, 19.65.

[0581]

[Referential Example 52]

1-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

In the same manner as in Referential Example 48, a reaction was conducted using methyl N-tert-butoxycarbonyltranexamate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride, whereby the title compound was obtained.

[0582]

^{1}H-NMR ($CDCl_3$) δ: 0.80-1.00(2H,m), 1.40-1.60(3H,m), 1.43(9H,s), 1.60-1.90(4H,m), 1.90-2.10(2H,m), 2.30-2.40(1H,m), 2.97(2H,m), 3.30-3.50(4H,m), 3.60-3.80(4H,m), 4.64(1H,br), 7.50-7.60(1H,m), 7.70-7.80(1H,m), 7.80-8.00(3H,m), 8.33 and 8.35(1H, each s).

MS (FAB) m/z: 564 [$(M+H)^+$, Cl^{35}], 566 [$(M+H)^+$, Cl^{37}].

[0583]

[Referential Example 53]

Methyl 4-(N-tert-butoxycarbonylaminomethyl)benzoate

In the same manner as in Referential Example 44, a reaction was conducted using 4-aminomethylbenzoic acid as a raw material, whereby the title compound was obtained.

[0584]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.91(3H,s), 4.37(2H,d,J=5.4Hz), 4.92(1H,br), 7.35(2H,d,J=8.3Hz), 8.00(2H,d,J=8.3Hz).

Elementary analysis for $C_{14}H_{19}NO_4$

Calculated: C, 63.38; H, 7.22; N, 5.28.

Found: C, 63.20; H, 7.02; N, 5.58.

[0585]

[Referential Example 54] 1-[4-(N-tert-Butoxycarbonylaminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 48, a reaction was conducted using methyl 4-(N-tert-butoxycarbonylaminomethyl)benzoate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride, whereby the title compound was obtained.

[0586]

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 3.00-3.30(4H,br), 3.40-4.00(4H,br), 4.31(2H,d,J=5.9Hz), 4.90(1H,br), 7.27(4H,m),

7.59(1H,dd,J=8.8,1.5Hz), 7.75(1H,d,J=8.8Hz), 7.90-8.00(3H,m), 8.30(1H,s).

MS (FAB) m/z: 544 [$(M+H)^+$, Cl^{35}], 546 [$(M+H)^+$, Cl^{37}].

[0587]

[Referential Example 55]

Methyl 3-(N-tert-butoxycarbonylaminomethyl)benzoate

Methyl 3-methylbenzoate (1.00 g) was dissolved in carbon tetrachloride (10 ml), followed by the addition of N-bromosuccinic imide (1.22 g) and 2,2′-azobisisobutyronitrile (catalytic amount). The resulting mixture was heated under reflux for 1 hour under exposure to a mercury lamp. After the insoluble matter was filtered off, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 20:1), whereby a colorless oil (1.34 g) was obtained.

The colorless oil (0.62 g) so obtained was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of sodium azide (0.38 g). The resulting mixture was stirred at room temperature for 20 hours. After the concentration of the reaction mixture under reduced pressure, the concentrate was diluted with ethyl acetate, washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (15 ml). Triphenylphosphine (0.75 g) was added to the resulting solution, followed by stirring at an external temperature of about 50°C for 5 hours. After the

addition of about 28% aqueous ammonia (7 ml) and stirring for further 2 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was extracted with ether. Dilute hydrochloric acid was added to the extract to make it acidic. To the water layer so separated, a dilute aqueous solution of sodium hydroxide was added to make it alkaline, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in dichloromethane (7 ml). To the resulting solution, di-tert-butyl dicarbonate (0.45 g) was added under ice cooling, followed by stirring at room temperature for 3 days. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 5:1), whereby the title compound (0.29 g, 35%) was obtained.

[0588]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 3.91(3H,s), 4.36(2H,d,J=5.9Hz), 4.97(1H,br), 7.40(1H,t,J=7.8Hz), 7.49(1H,d,J=7.8Hz), 7,90-8.00(2H,m).

MS (FAB) m/z: 266 $(M+H)^+$.

[0589]

[Referential Example 56]

Methyl 4-cyanomethylbenzoate

In dichloromethane (20 ml), methyl 4-hydroxymethylbenzoate (1.00 g) was dissolved, followed by the

addition of triethylamine (0.9 ml). Under ice cooling, a solution of methanesulfonyl chloride (0.70 g) in dichloromethane (dichloromethane: 5 ml) was added to the resulting solution. The resulting mixture was stirred at room temperature for 15 hours. After dilution with dichloromethane, the reaction mixture was washed with water and was then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in acetonitrile (12 ml). To the resulting solution, potassium cyanide (0.80 g) and 18-Crown-6 (0.16 g) were added, followed by stirring at room temperature for 40 hours. After concentration under reduced pressure, the concentrate was diluted with dichloromethane, washed with water and then, dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane), whereby colorless crystals (0.91 g, 86%) was obtained. A portion of the resulting crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

[0590]

^{1}H-NMR ($CDCl_3$) δ: 3.82(2H,s), 3.93(3H,s), 7.42(2H,d,=8.3Hz), 8.06(2H,d,J=8.3Hz).

Elementary analysis for $C_{10}H_9NO_2$

Calculated: C, 68.56; H, 5.18; N, 8.00.

Found: C, 68.39; H, 5.29; N, 8.08.

[0591]

[Referential Example 57]

Methyl 4-[2-(tert-butoxycarbonylamino)ethyl]benzoate

Methyl 4-cyanomethylbenzoate (0.20 g) was dissolved in a mixed solvent of methanol (15 ml) and chloroform (0.4 ml). To the resulting solution, platinum dioxide (33 mg) was added, followed by catalytic reduction at room temperature under 3 atmospheric pressure for 3 hours. The catalyst was removed by filtration through Celite and the solvent was distilled off under reduced pressure. The residue was suspended in dichloromethane (5 ml), followed by the addition of triethylamine (160 µl). After the addition of a solution of di-tert-butyl dicarbonate (0.29 g) in dichloromethane (dichloromethane: 2 ml) under ice cooling, the resulting solution was stirred at room temperature for 13 hours. The reaction mixture was diluted with dichloromethane, washed with water and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 ~ 5:1), whereby the title compound (0.28 g, 88%) was obtained.

[0592]

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 2.86(2H,t,J=6.8Hz), 3.39(2H,m), 3.91(3H,s), 4.53(1H,br), 7.27(2H,d,J=8.3Hz),

7.98(2H,d,J=8.3Hz).

Elementary analysis for $C_{15}H_{21}NO_4$

Calculated: C, 64.50; H, 7.58; N, 5.01.

Found: C, 64.43; H, 7.35; N, 4.97.

[0593]

[Referential Example 58]

1-[4-[2-(tert-Butoxycarbonylamino)ethyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 48, the title compound was obtained using methyl 4-[2-(tert-butoxycarbonylamino)ethyl]benzoate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0594]

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 2.79(2H,t,J=6.8Hz), 3.10(4H,br), 3.35(2H,m), 3.40-4.00(4H,br), 4.50(1H,br), 7.18(2H,d,J=8.3Hz), 7.24(2H,d,J=8.3Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,2.0Hz), 7.90-8.00(3H,m), 8.30(1H,s).

MS (FAB) m/z: 558 [$(M+H)^+$, Cl^{35}], 560 [$(M+H)^+$, Cl^{37}].

[0595]

[Referential Example 59]

Methyl 4-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In tetrahydrofuran (50 ml), methyl 4-hydroxybenzoate (1.01 g), (3R)-1-tert-butoxycarbonyl-3-pyrrolidinole (1.36 g)

and triphenylphosphine (1.73 g) were dissolved, followed by the dropwise addition of a 40% solution (2.87 ml) of diethyl azodicarboxylate in toluene under ice cooling. The resulting mixture was stirred at room temperature for 20 hours. To the reaction mixture, ethyl acetate and a 10% aqueous solution of potassium carbonate were added and the organic layer was collected. The resulting organic layer was washed with a 10% aqueous solution of potassium carbonate and water and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (1.60 g, 76%) was obtained.

[0596]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 2.00-2.20(2H,m), 3.40-3.70(4H,m), 3.89(3H,s), 4.96(1H,br s), 6.88(2H,d,J=8.8Hz), 7.90-8.00(2H,m).

[0597]

[Referential Example 60]

4-[[(3S)-1-tert-Butoxycarbony-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, a reaction was conducted using methyl 4-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a raw material, whereby the title compound was obtained.

^{1}H-NMR (CD_3OD) δ: 1.45 and 1.47(9H, each s), 2.10-2.20(2H,m),

3.40-3.70(4H,m), 5.00-5.10(1H,m), 6.98(2H,d,J=8.8Hz), 7.97(2H,d,J=8.8Hz).

[0598]

[Referential Example 61]

1-[4-[[(3S)-1-tert-Butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0599]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 2.00-2.20(2H,m), 3.00-3.20(4H,m), 3.40-3.80(8H,m), 4.88(1H,br s), 6.82(2H,d,J=8.3Hz), 7.20-7.30(2H,m), 7.60(1H,dd,J=8.7,1.9Hz), 7.76(1H,dd,J=8.5,1.7Hz), 7.90-7.95(3H,m), 8.30(1H,s).

Elementary analysis for $C_{30}H_{34}ClN_3O_6S$

Calculated: C, 60.04; H, 5.71; N, 7.00.

Found: C, 60.05; H, 5.69; N, 6.80.

[0600]

[Referential Example 62]

Methyl 3-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, a reaction was conducted using methyl 3-hydroxybenzoate as a raw material,

whereby the title compound was obtained.

[0601]

^{1}H-NMR ($CDCl_3$)δ: 1.45 and 1.47(9H, each s), 2.05-2.25(2H,m), 3.40-3.70(4H,m), 3.92(3H,s), 4.96(1H,br s), 7.07(1H,d,J=7.8Hz), 7.30-7.40(1H,m), 7.53(1H,d,J=2.0Hz), 7.65(1H,m).

MS (FAB) m/z: 322 $(M+H)^+$.

[0602]

[Referential Example 63]

3-[[(3S)-1-tert-Butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl 3-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a raw material.

[0603]

^{1}H-NMR (CD_3OD) δ: 1.45 and 1.47(9H, each s), 2.05-2.25(2H,m), 3.35-3.65(4H,m), 5.04(1H,br s), 7.05-7.15(1H,m), 7.30-7.40(1H,m), 7.53(1H,s), 7.62(1H,d,J=7.3Hz).

MS (FAB) m/z: 308 $(M+H)^+$.

[0604]

[Referential Example 64]

1-[3-[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title

compound was obtained using 3-[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a raw material.

[0605]

^{1}H-NMR ($CDCl_3$) δ: 1.45 and 1.46(9H, each s), 2.00-2.20(2H,m), 2.95-3.25(4H,m), 3.40-3.90(8H,m), 4.84(1H,br s), 6.80-6.90(3H,m), 7.20-7.30(1H,m), 7.60(1H,dd,J=8.8,1.5Hz), 7.76(1H,dd,J=8.5,1.7Hz), 7.90-7.95(3H,m), 8.30-8.35(1H,m).

MS (FAB) m/z: 600 [$(M+H)^+$, Cl^{35}], 602 [$(M+H)^+$, Cl^{37}].

[0606]

[Referential Example 65]

Methyl 4-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, the title compound was obtained using methyl 4-hydroxybenzoate and (3S)-1-tert-butoxycarbonyl-3-pyrrolidinole as raw materials.

[0607]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.05-2.25(2H,m), 3.4-3.7(4H,m), 3.89(3H,s), 4.96(1H,br s), 6.88(2H,d,J=8.8Hz), 7.90-8.00(2H,m).

MS (FAB) m/z: 322 $(M+H)^+$.

[0608]

[Referential Example 66]

4-[[(3R)-1-tert-Butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the title

compound was obtained using methyl 4-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a raw material.

[0609]

^{1}H-NMR (CD_3OD) δ: 1.47 and 1.48(9H, each s), 2.10-2.25(2H,m), 3.40-3.70(4H,m), 4.98(1H,br s), 6.91(2H,d,J=8.8Hz), 8.00-8.10(2H,m).

MS (FAB) m/z: 308 $(M+H)^+$.

[0610]

[Referential Example 67]

1-[4-[[(3R)-1-tert-Butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained using 4-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a raw material.

[0611]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 2.00-2.20(2H,m), 3.00-3.20(4H,m), 3.40-3.80(8H,m), 4.89(1H,br s), 6.82(2H,d,J=8.3Hz), 7.20-7.30(2H,m), 7.58(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.5,1.7Hz), 7.90-7.95(3H,m), 8.30(1H,s).

MS (FAB) m/z: 600 [$(M+H)^+$, Cl^{35}], 602 [$(M+H)^+$, Cl^{37}].

[0612]

[Referential Example 68]

Methyl 3-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, the title compound was obtained using methyl 3-hydroxybenzoate and (3S)-1-tert-butoxycarbonyl-3-pyrrolidinole as raw materials.

[0613]

^{1}H-NMR ($CDCl_3$)δ: 1.47(9H,s), 2.05-2.25(2H,m), 3.40-3.70(4H,m), 3.92(3H,s), 4.95(1H,br s), 7.07(1H,d,J=7.8Hz), 7.30-7.40(1H,m), 7.50-7.55(1H,m), 7.60-7.70(1H,m).

MS (FAB) m/z: 322 $(M+H)^+$.

[0614]

[Referential Example 69]

3-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl 3-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a raw material.

[0615]

^{1}H-NMR (CD_3OD) δ: 1.48(9H,s), 2.05-2.25(2H,m), 3.45-3.70(4H,m), 4.97(1H,br s), 7.10-7.15(1H,m), 7.35-7.45(1H,m), 7.58(1H,s), 7.70-7.75(1H,m).

MS (FAB) m/z: 308 $(M+H)^+$.

[0616]

[Referential Example 70]

1-[3-[[(3R)-1-tert-Butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained using 3-[[(3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a raw material.

[0617]

^{1}H-NMR ($CDCl_3$) δ: 1.45 and 1.46(9H, each s), 2.00-2.20(2H,m), 2.95-3.25(4H,m), 3.40-3.90(8H,m), 4.84(1H,br s), 6.80-6.90(3H,m), 7.20-7.30(1H,m), 7.60(1H,dd,J=8.5,1.7Hz), 7.76(1H,dd,J=8.5,2.0Hz), 7.90-7.95(3H,m), 8.30-8.35(1H,m).

MS (FAB) m/z: 600 [$(M+H)^+$, Cl^{35}], 602 [$(M+H)^+$, Cl^{37}].

[0618]

[Referential Example 71]

4-[2-Amino-5-pyrimidyl)benzoic acid

In the same manner as in Referential Example 2, the title compound was obtained using 2-amino-5-bromopyrimidine as a raw material.

[0619]

^{1}H-NMR (DMSO-d_6) δ: 7.81(2H,d,J=8.8Hz), 8.00(2H,d,J=8.8Hz), 8.84(2H,s).

MS (FAB) m/z: 216 $(M+H)^+$.

[0620]

[Referential Example 72]

1-tert-Butoxycarbonyl-4-[(methoxycarbonyl)methylene]piperidine

In tetrahydrofuran (40 ml), methyl dimethylphosphonoacetate (1.8 ml) was dissolved. To the

resulting solution, 60% oily sodium hydride (450 mg) was added under ice cooling, followed by stirring under the same condition. After the addition of a solution of 1-(tert-butoxycarbonyl)-4-piperidone (2.05 g) in tetrahydrofuran (tetrahydrofuran: 10 ml) and stirring at room temperature for 30 minutes, the reaction mixture was diluted with ethyl acetate. To the diluted solution, 2N hydrochloric acid was added. The organic layer was collected, washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous saline, and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 6:1), whereby the title compound (2.35 g, 92%) was obtained.

[0621]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.28(2H,t,J=5.9Hz), 2.94(2H,t,J=5.9Hz), 3.48(2H,t,J=5.9Hz), 3.50(2H,t,J=5.9Hz), 3.70(3H,s), 5.72(1H,s).

Elementary analysis for $C_{13}H_{21}NO_4$

Calculated: C, 61.16; H, 8.29; N, 5.49.

Found: C, 61.14; H, 8.34; N, 5.20.

[0622]

[Referential Example 73]

Methyl (1-tert-butoxycarbonylpiperidin-4-yl)acetate

In ethanol (10 ml), 1-tert-butoxycarbonyl-4-[(methoxycarbonyl)methylene]piperidine (875 mg) was dissolved, followed by the addition of 10% palladium carbon (water content:

about 50%, 730 mg). The resulting mixture was subjected to catalytic reduction under normal pressure at room temperature for 3 days. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure, whereby the title compound (871 mg, 99%) was obtained.

[0623]

^{1}H-NMR ($CDCl_3$) δ: 1.16(2H,m), 1.45(9H,s), 1.65(2H,m), 1.93(1H,m), 2.25(2H,d,J=6.8Hz), 2.72(2H,br), 3.68(3H,s), 4.08(2H,br).

MS (FAB) m/z: 258 $(M+H)^+$.

[0624]

[Referential Example 74]

(1-tert-Butoxycarbonylpiperidin-4-yl)acetic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl (1-tert-butoxycarbonylpiperidin-4-yl)acetate as a raw material.

[0625]

^{1}H-NMR ($CDCl_3$) δ: 1.18(2H,m), 1.45(9H,s), 1.73(2H,m), 1.94(1H,m), 2.29(2H,d,J=6.8Hz), 2.72(2H,m), 4.10(2H,br).

MS (EI) m/z: 243 M^+.

[0626]

[Referential Example 75]

1-[(1-tert-Butoxycarbonylpiperidin-4-yl)acetyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction

was conducted using (1-tert-butoxycarbonylpiperidin-4-yl)acetic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0627]

^{1}H-NMR ($CDCl_3$) δ: 1.05(2H,m), 1.43(9H,s), 1.63(2H,m), 1.91(1H,m), 2.14(2H,d,J=6.8Hz), 2.66(2H,m), 3.07(4H,br s), 3.56(2H,br s), 3.67(2H,br s), 4.02(2H,br), 7.58(1H,dd,J=8.8,2.0Hz), 7.75(1H,d,J=8.8Hz), 7.91(1H,d,J=8.8Hz), 7.93(1H,d,J=8.8Hz), 7.92(1H,s), 8.30(1H,s).

MS (FAB) m/z: 536 [$(M+H)^+$, Cl^{35}], 538 [$(M+H)^+$, Cl^{37}].

[0628]

[Referential Example 76]

3-(1-tert-Butoxycarbonylpiperidin-4-yl)propionic acid

Ethyl 1-tert-butoxycarbonylisonipecotinate was used as a raw material and diisobutylaluminum hydride was used, whereby the corresponding aldehyde derivative was obtained. The resulting derivative was treated as in Referential Examples 72, 73 and 74, whereby the title compound was obtained.

[0629]

^{1}H-NMR ($CDCl_3$) δ: 1.10(2H,m), 1.41(1H,m), 1.45(9H,s), 1.60(2H,q,J=7.8Hz), 1.66(2H,m), 2.39(2H,t,J=7.8Hz), 2.67(2H,m), 4.09(2H,br).

MS (FAB) m/z: 258 $(M+H)^+$.

[0630]

[Referential Example 77]

1-[3-(1-tert-Butoxycarbonylpiperidin-4-yl]propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 3-(1-tert-butoxycarbonylpiperidin-4-yl)propionic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0631]

^{1}H-NMR ($CDCl_3$) δ: 1.04(2H,m), 1.35(1H,m), 1.44(9H,s), 1.47(2H,q,J=7.8Hz), 1.57(2H,m), 2.24(2H,t,J=7.8Hz), 2.61(2H,m), 3.07(4H,br s), 3.56(2H,br s), 3.71(2H,br s), 4.04(2H,br), 7.58(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,2.0Hz), 7.90(1H,d,J=8.8Hz), 7.91(1H,s), 7.92(1H,d,J=8.8Hz), 8.30(1H,s).

MS (FAB) m/z: 550 [$(M+H)^+$, Cl^{35}], 552 [$(M+H)^+$, Cl^{37}].

[0632]

[Referential Example 78]

(E)-3-(4-Pyridyl)acrylic acid

In the same manner as in Referential Example 72 or 74, the title compound was obtained using isonicotinic aldehyde as a raw material.

[0633]

^{1}H-NMR (DMSO-d_6) δ: 6.79(1H,d.J=16.6Hz), 7.56(1H,d,J=16.6Hz),

7.66(2H,d,J=5.9Hz), 8.62(2H,d,J=5.9Hz), 12.72(1H,br s).

MS (EI) m/z: 149M$^+$.

[0634]

[Referential Example 79]

1-Methoxycarbonyl-3-pyrroline

In dichloromethane (20 ml), 3-pyrroline (1.1 ml) was dissolved, followed by the addition of triethylamine (2.6 ml) and methyl chloroformate (1.2 ml) under ice cooling. The resulting mixture was stirred at room temperature for 17 hours. The residue obtained by distilling the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (0.95 g, 52%) was obtained.

[0635]

^{1}H-NMR ($CDCl_3$) δ: 3.73(3H,s), 4.00-4.20(4H,m), 5.70-5.90(2H,m).

[0636]

[Referential Example 80]

Methyl 4-trifluoromethanesulfonyloxybenzoate

In dichloromethane (20 ml), methyl 4-hydroxybenzoate (1.99 g) was dissolved, followed by the addition of pyridine (2.4 ml) and trifluoromethanesulfonic anhydride (3.0 ml) under ice cooling. After stirring at room temperature for 6 hours, the reaction mixture was added with pyridine (1.5 ml) and trifluoromethanesulfonic anhydride (1.0 ml) again. The resulting mixture was stirred for 5 hours. Dichloromethane and an aqueous solution of sodium bicarbonate were added to the

reaction mixture. The organic layer so separated was washed with a 10% aqueous citric acid solution and saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (5% ethyl acetate - hexane), whereby the title compound (3.22 g, 86%) was obtained.

[0637]

^{1}H-NMR ($CDCl_3$) δ: 3.95(3H,s), 7.36(2H,d,J=8.8Hz), 8.15(2H,d,J=8.8Hz).

MS (FAB) m/z: 285 $(M+H)^+$.

[0638]

[Referential Example 81]

Methyl 4-(1-methoxycarbonylpyrrolidin-3-yl)benzoate

In N,N-dimethylformamide (25 ml), methyl 4-trifluoromethanesulfonyloxybenzoate (1.05 g), 1-methoxycarbonyl-3-pyrroline (1.0 g), lithium chloride (0.51 g), palladium (II) acetate(53 mg) and tri(2-furyl)phosphine (100 mg) were dissolved, followed by the addition of diisopropylethylamine (2.8 ml). Under an argon gas atmosphere, the resulting mixture was stirred at 90°C for 11 hours and then, at 100°C for 7 hours. The residue obtained by distilling off the solvent under reduced pressure was added with dichloromethane and water. The organic layer collected by separation was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced

pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 9:1 ~ 5:1). The purified product was dissolved in methanol (30 ml), followed by the addition of 10% palladium carbon (water content: about 50%, 186 mg) and ammonium formate (197 mg). The resulting mixture was heated under reflux for 2 hours. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (10% ethyl acetate - toluene), whereby the title compound (241 mg, 25%) was obtained.

[0639]

^{1}H-NMR ($CDCl_3$) δ: 1.95-2.10(1H,m), 2.25-2.35(1H,m), 3.30-3.35(4H,m), 3.55-3.75(1H,m), 3.72 and 3.73(3H, each s), 3.80-3.90(1H,m), 3.91(3H,s), 7.30(2H,d,J=3.8Hz), 8.00(2H,d,J=8.3Hz).

MS (FAB) m/z: 264 $(M+H)^+$.

[0640]

[Referential Example 82]

4-(1-tert-Butoxycarbonylpyrrolidin-3-yl)benzoic acid

In methanol (10 ml), methyl 4-(1-methoxycarbonylpyrrolidin-3-yl)benzoate (0.24 g) was dissolved. The resulting solution was added with 8N hydrochloric acid (30 ml), followed by heating under reflux for 40 hours. The residue obtained by distilling off the solvent under reduced pressure was dissolved in N,N-dimethylformamide

(30 ml). To the resulting solution, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.30 g) and then diisopropylethylamine (0.40 ml) were added, followed by stirring at room temperature for 15 hours. The residue obtained by distilling off the solvent under reduced pressure was distributed in ethyl acetate and a 10% aqueous citric acid solution. The organic layer collected by separation was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 10% methanol - dichloromethane), whereby the title compound (234 mg) was obtained.

[0641]

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,m), 1.90-2.00(1H,m), 2.20-2.30(1H,m), 3.20-3.90(5H,m), 7.20-7.30(2H,m), 8.00-8.10(2H,m).

MS (EI) m/z: 291M$^+$.

[0642]

[Referential Example 83]

1-[4-(3RS)-1-tert-Butoxycarbonylpyrrolidin-3-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-butoxycarbonylpyrrolidin-3-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0643]

^{1}H-NMR ($CDCl_3$) δ: 1.47 and 1.60(9H, each s), 1.80-2.00(1H,m), 2.1-2.2(1H,m), 3.0-4.0(13H,m), 7.10-7.30(4H,m), 7.55-7.65(1H,m), 7.7-7.8(1H,m), 7.85-8.00(3H,m), 8.30(1H,s).

[0644]

[Referential Example 84]

(3S)-3-Amino-1-tert-butoxycarbonylpyrrolidine

In the same manner as in Referential Example 55, the title compound was obtained using (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypyrrolidine (1.50 g) as a raw material.

[0645]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.98-2.11(2H,m), 2.95-3.10(1H,m), 3.26-3.60(4H,m).

MS (FAB) m/z: 187 $(M+H)^+$.

[0646]

[Referential Example 85]

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]pyrrolidine trifluoroacetate

In the same manner as in Referential Example 1, a reaction was conducted using (3S)-3-amino-1-tert-butoxycarbonylpyrrolidine as a raw material, whereby the title compound was obtained.

[0647]

^{1}H-NMR (DMSO-d_6) δ: 1.69-1.80(1H,m), 1.88-1.99(1H,m), 2.95-3.28(4H,m), 3.75-3.84(1H,m), 7.71(1H,m), 7.91(1H,m), 8.10-

8.30(4H,m), 8.53(1H,s), 8.91(1H,br s), 9.06(1H,br s).

[0648]

[Referential Example 86]

(3S)-3-Amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In trifluoroacetic acid, (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypryrrolidine was dissolved. After the resulting solution was concentrated under reduced pressure, diethyl ether was added to the concentrate, followed by the removal of the supernatant. The residue was reacted as in Referential Example 1, whereby the corresponding sulfonamide derivative was obtained as a crude product. The crude product was subjected to azide formation and reduction as in Referential Example 55, whereby the title compound was obtained.

[0649]

^{1}H-NMR (DMSO-d_6) δ: 1.38-1.53(3H,m), 1.72-1.83(1H,m), 2.81-2.89(1H,m), 3.20-3.39(4H,m), 7.69(1H,dd,J=8.8,1.9Hz), 7.87(1H,d,J=8.8Hz), 8.12(1H,d,J=8.8Hz), 8.21(1H,s), 8.26(1H,d,J=8.8Hz), 8.39(1H,s).

MS (FAB) m/z: 311 [$(M+H)^+$, Cl^{35}], 313 [$(M+H)^+$, Cl^{37}].

[0650]

[Referential Example 87]

4-Benzylamino-1-tert-butoxycarbonylpiperidine

In dichloromethane (500 ml), 1-tert-butoxycarbonyl-4-piperidione (7.00 g) was dissolved, followed by the addition of benzylamine (4.03 ml) and sodium triacetoxyborohydride

(11.91 g). The resulting mixture was stirred overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate. The resulting mixture was washed with water and saturated saline and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (7.46 g, 76%) was obtained.

[0651]

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.37(2H,m), 1.45(9H,s), 1.80-1.90(2H,m), 2.62-2.70(1H,m), 2.75-2.85(1H,m), 2.98-3.07(1H,m), 3.78-3.90(3H,m), 3.95-4.10(1H,m), 7.21-7.34(5H,m).

MS (FD) m/z: 290M$^+$.

[0652]

[Referential Example 88]

4-Amino-1-tert-butoxycarbonylpiperidine acetate

In methanol (2 ml) and acetic acid (30 ml), 4-benzylamino-1-tert-butoxycarbonylpiperidine (4.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 3.06 g). The resulting mixture was subjected to catalytic reduction overnight under medium pressure (3 atmospheric pressure). After the removal of the catalyst by filtration, the filtrate was distilled off under reduced pressure. The residue was solidified in ethyl acetate, whereby the title compound (2.23 g, 57%) was obtained.

[0653]

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.23(2H,m), 1.39(9H,s), 1.69-1.77(2H,m), 1.80(3H,s), 2.50(2H,s), 2.67-2.88(2H,m), 3.80-3.90(1H,m).

Elementary analysis for $C_{10}H_{20}N_2O_2 \cdot CH_3CO_2H$

Calculated: C, 53.16; H, 9.37; N, 10.33.

Found: C, 53.51; H, 9.10; N, 9.93.

[0654]

[Referential Example 89]

4-[(6-Chloronaphthalen-2-yl)sulfonamido]piperidine trifluoroacetate

In the same manner as in Referential Example 1, the title compound was obtained using 4-amino-1-tert-butoxycarbonylpiperidine acetate and 6-chloro-2-naphthylsulfonyl chloride as raw materials.

[0655]

^{1}H-NMR (DMSO-d_6) δ: 1.47-1.60(2H,m), 1.68-1.78(2H,m), 2.81-2.95(2H,m), 3.10-3.20(2H,m), 3.29-3.40(1H,m), 7.70(1H,dd,J=8.8,2.0Hz), 7.91(1H,dd,J=8.8,2.0Hz), 8.11-8.15(2H,m), 8.21(1H,s), 8.31(1H,br s), 8.50(1H,s), 8.55(1H,br s).

MS (FAB) m/z: 325 [$(M+H)^+$, Cl^{35}], 327 [$(M+H)^+$, Cl^{37}].

[0656]

[Referential Example 90]

Ethyl (1RS)-4-trifluoromethanesulfonyloxy-3-

cyclohexenecarboxylate

Diisopropylamine (0.99 ml) was dissolved in tetrahydrofuran (50 ml), followed by the dropwise addition of n-butyl lithium (a 1.59M hexane solution, 3.70 ml) at -78°C. After the dropwise addition of ethyl 4-oxocyclohexanecarboxylate (1.00 g) dissolved in tetrahydrofuran (5 ml) to the reaction mixture and stirring for 15 minutes, N-phenyltrifluoromethanesulfonimide (2.10 g) dissolved in tetrahydrofuran (5 ml) was added dropwise to the reaction mixture. The reaction mixture was heated to 0°C, stirred for one hour and then concentrated under reduced pressure. The residue was purified by chromatography on a neutral alumina column (hexane : ethyl acetate = 9:1), whereby the title compound (838 mg, 47%) was obtained.

[0657]

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.3Hz), 1.88-1.99(1H,m), 2.10-2.18(1H,m), 2.38-2.50(4H,m), 2.55-2.64(1H,m), 4.16(2H,q,J=7.3Hz), 5.77(1H,br s).

MS (FAB) m/z: 303 $(M+H)^+$.

[0658]

[Referential Example 91]

Ethyl (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylate

In the same manner as in Referential Example 7, reaction was effected using ethyl (1RS)-4-trifluoromethanesulfonyloxy-3-cyclohexenecarboxylate as a raw material, whereby the title compound was obtained.

[0659]

^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.3Hz), 1.80-1.91(1H,m), 2.19-2.25(1H,m), 2.40-2.57(4H,m,), 2.59-2.67(1H,m), 4.17(2H,q,J=7.3Hz), 6.36(1H,br s), 7.26(2H,dd,J=4.9,1.5Hz), 8.53(2H,dd,J=4.9,1.5Hz).

MS (FAB) m/z: 232 $(M+H)^+$.

[0660]

[Referential Example 92]

(1RS)-4-(4-Pyridyl)-3-cyclohexenecarboxylic acid

In the same manner as in Referential Example 8, reaction was effected using ethyl (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylate as a raw material, the title compound was obtained.

[0661]

^{1}H-NMR (DMSO-d_6) δ: 1.70-1.82(1H,m), 2.10-2.19(1H,m), 2.42-2.65(5H,m), 6.99(1H,br s), 8.02(2H,d,J=6.8Hz), 8.80(2H,d,J=6.8Hz).

MS (FAB) m/z: 204 $(M+H)^+$.

[0662]

[Referential Example 93]

cis-, trans-4-(4-Pyridyl)cyclohexanecarboxylic acid

In the same manner as in Referential Example 73 by using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid as a raw material, the title compound was obtained.

MS (FAB) m/z: 206 $(M+H)^+$.

[0663]

[Referential Example 94]

4-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid

In 1,2-dimethoxyethane (30 ml), 4-(1-tert-butoxycarbonyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (Synthesis, 993, 1991) (3.59 g) was dissolved, followed by the addition of 4-carboxyphenylboric acid (3.60 g), lithium chloride (1.38 g), tetrakistriphenylphosphine palladium (0.62 g) and an aqueous solution of sodium carbonate (2M, 16.3 ml). The resulting mixture was heated under reflux for 2 hours under an argon gas atmosphere. To the reaction mixture, 1N hydrochloric acid was added. The resulting mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1). The purified product was pulverized and washed in a mixed solvent of hexane and ethyl acetate (hexane : ethyl acetate = 5:1), whereby the title compound (462 mg, 14%) was obtained.

[0664]

^{1}H-NMR ($CDCl_3$) δ: 1.50(9H,s), 2.56(2H,br s), 3.66(2H,m), 4.12(2H,br s), 6.19(1H,br s), 7.47(2H,d,J=8.3Hz), 8.07(2H,d,J=8.3Hz).

MS (FAB) m/z: 304 $(M+H)^+$.

[0665]

[Referential Example 95]

4-(1-tert-Butoxycarbonylpiperidin-4-yl)benzoic acid

In the same manner as in Referential Example 73, the title compound was obtained using 4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid as a raw material.

[0666]

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 1.60-1.71(2H,m), 1.80-1.89(2H,m), 2.69-2.90(3H,m), 4.20-4.35(2H,m), 7.31(2H,d,J=8.3Hz), 8.05(2H,d,J=8.3Hz).

MS (FAB) m/z: 306 $(M+H)^+$.

[0667]

[Referential Example 96]

1-[4-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0668]

^{1}H-NMR ($CDCl_3$) δ: 1.49(9H,s), 2.48(2H,br s), 3.10(4H,br), 3.62(2H,t,J=5.9Hz), 3.70(4H,br), 4.08(2H,br s), 6.05(1H,br s), 7.25(2H,d,J=8.3Hz), 7.34(2H,d,J=8.3Hz),

7.59(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,2.0Hz), 7.90-7.96(3H,m), 8.30(1H,s).

MS (FAB) m/z: 596 [$(M+H)^+$, Cl^{35}], 598 [$(M+H)^+$, Cl^{37}].

[0669]

[Referential Example 97]

1-[4-(1-tert-Butoxycarbonylpiperidin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-butoxycarbonylpiperidin-4-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0670]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.49-1.63(2H,m), 1.72-1.80(2H,m), 2.59-2.68(1H,m), 2.71-2.86(2H,m), 2,92-3.30(4H,m), 3.45-4.95(4H,m), 4.16-4.31(2H,m), 7.18(2H,d,J=8.3Hz), 7.24(2H,d,J=8.3Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,2.0Hz), 7.90-7.94(3H,m), 8.30(1H,s).

MS (FAB) m/z: 598 [$(M+H)^+$, Cl^{35}], 600 [$(M+H)^+$, Cl^{37}].

[0671]

[Referential Example 98]

(3RS)-3-Amino-1-tert-butoxycarbonylpyrrolidine

In methanol (30 ml), 3-aminopyrrolidine (0.54 g) was dissolved under ice cooling, followed by the addition of diisopropylethylamine (720 µl) and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.84 g). The

resulting mixture was gradually heated to room temperature and stirred for 11 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 5% methanol - dichloromethane), whereby the title compound (0.59 g, 94%) was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.0-2.3(2H,m), 3.1-4.0(5H,m).

[0672]

[Referential Example 99]

(3RS)-1-tert-Butoxycarbonyl-3-[(6-chloronaphthalen-2-yl)sulfonamide]pyrrolidine

In the same manner as in Referential Example 1, the title compound was obtained using (3RS)-3-amino-1-tert-butoxycarbonylpyrrolidine as a raw material.

^{1}H-NMR ($CDCl_3$) δ: 1.37(9H,s), 1.60-2.10(2H,m), 3.00-3.50(4H,m), 3.88(1H,br), 4.96(1H,br), 7.50-7.60(1H,m), 7.80-7.90(4H,m), 8.43(1H,s).

MS (FAB) m/z: 411 [$(M+H)^+$, Cl^{35}], 413 [$(M+H)^+$, Cl^{37}].

[0673]

[Referential Example 100]

(3RS)-1-tert-Butoxycarbonyl-3-[4-(4-pyridyl)benzamide]pyrrolidine

In the same manner as in Referential Example 12, the title compound was obtained using (3RS)-3-amino-1-tert-butoxycarbonylpyrrolidine and 4-(4-pyridyl)benzoic acid as raw

materials.

[0674]

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s); 1.90-2.10(1H,m), 2.20-2.30(1H,m), 3.30-3.40(1H,m), 3.40-3.60(2H,m), 3.70-3.80(1H,m), 4.65-4.75(1H,m), 6.25-6.35(1H,m), 7.52(2H,d,J=5.9Hz), 7.71(2H,d,J=8.3Hz), 7.88(2H,d,J=8.3Hz), 8.70(2H,d,J=5.4Hz).
MS (FAB) m/z: 368 $(M+H)^+$.

[0675]

[Referential Example 101]

6-Chloro-N-methoxy-N-methylnicotinamide

Under ice cooling, 6-chloronicotinic acid (5.00 g) was suspended in dichloromethane (150 ml), followed by the addition of a catalytic amount of N,N-dimethylformamide and oxalyl chloride (5.30 ml). The resulting mixture was stirred at room temperature for 23 hours. The residue obtained by concentrating the reaction mixture was dissolved in dichloromethane (100 ml), followed by the addition of N,O-dimethylhydroxylamine hydrochloride (6.18 g) and triethylamine (13.3 ml) under ice cooling. After stirring at room temperature for 6 hours, the reaction mixture was diluted with dichloromethane (150 ml), washed with a saturated aqueous solution of sodium bicarbonate, water and saturated saline and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (6.08 g, 96%)

was obtained.

[0676]

^{1}H-NMR ($CDCl_3$) δ: 3.39(3H,s), 3.56(3H,s), 7.39(1H,d,J=8.3Hz), 8.03(1H,dd,J=8.3,2.4Hz), 8.78(1H,d,J=2.4Hz).

[0677]

[Referential Example 102] 6-Chloronicotinaldehyde

In tetrahydrofuran (8 ml), 6-chloro-N-methoxy-N-methylnicotinamide (500 mg) was dissolved, followed by the dropwise addition of diisobutylaluminum hydride (a 0.95M hexane solution, 2.88 ml) at -78°C in an argon gas atmosphere. The resulting mixture was stirred for 3 hours and then, at room temperature, for 2 hours. After the reaction mixture was cooled to -20°C, saturated saline (2 ml) was added thereto, followed by stirring for 30 minutes. The insoluble matter was filtered off. The residue was washed with ethyl acetate. The filtrate and the washing were combined together. The mixture was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, whereby the title compound (346 mg, 98%) was obtained as a crude product. The product was provided for the subsequent reaction without purification.

[0678]

^{1}H-NMR ($CDCl_3$) δ: 7.52(1H,d,J=8.3Hz), 8.14(1H,dd,J=8.3,2.2Hz), 8.87(1H,d,J=2.2Hz), 10.10(1H,s).

[0679]

[Referential Example 103]

1-tert-Butoxycarbonyl-4-methanesulfonylpiperazine

In dichloromethane (40 ml), N-tert-butoxycarbonylpiperazine (2.00 g) was dissolved, followed by the addition of triethylamine (1.78 ml). To the resulting mixture, methanesulfonyl chloride (0.91 ml) was added dropwise under ice cooling. After stirring for one hour under ice cooling, the reaction mixture was diluted with dichloromethane (20 ml), washed with a 5% aqueous citric acid solution, water and saturated saline and dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was recrystallized from a mixed solvent of ethyl acetate and hexane, whereby the title compound (2.58 g, 91%) was obtained.

[0680]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.79(3H,s), 3.19(4H,t,J=5.1Hz), 3.55(4H,t,J=5.1Hz).

[0681]

[Referential Example 104]

1-tert-Butoxycarbonyl-4-[[(2RS)-2-(6-chloropyridin-3-yl)-2-hydroxyethyl]sulfonyl]piperazine

In tetrahydrofuran (8 ml), 1-tert-butoxycarbonyl-4-methanesulfonylpiperazine (838 mg) was dissolved, followed by the addition of tert-butyl lithium (a 1.7M pentane solution, 1.72 ml) at -78°C in an argon gas atmosphere. The resulting mixture was stirred for 2 hours. After the dropwise addition

of a solution of 6-chloronicotinaldehyde (346 mg) in tetrahydrofuran (tetrahydrofuran: 4 ml) and stirring at -78°C for 3 hours, the reaction mixture was added with isopropanol (1 ml). The resulting mixture was heated to room temperature and diluted with ethyl acetate. The diluted solution was washed with water and saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was recrystallized from ethyl acetate, whereby the title compound (532 mg, 54%) was obtained.

[0682]

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 3.11(1H,dd,J=14.1,2.2Hz), 3.21(1H,dd,J=14.1,9.8Hz), 3.23-3.33(4H,m), 3.52-3.57(4H,m), 3.70(1H,br s), 5.37(1H,br), 7.36(1H,d,J=8.3Hz), 7.72(1H,dd,J=8.3,2.4Hz), 8.41(1H,d,J=2.4Hz).

MS (FAB) m/z: 405 $(M+H)^+$.

[0683]

[Referential Example 105]

1-tert-Butoxycarbonyl-4-[[(E)-2-(6-chloropyridin-3-yl)ethylene]sulfonyl]piperazine

In dichloromethane (10 ml), 1-tert-butoxycarbonyl-4-[[(2RS)-2-(6-chloropyridin-3-yl)-2-hydroxyethyl]sulfonyl]piperazine (465 mg) was dissolved, followed by the addition of N-methylmorpholine (0.152 ml) and N,N-dimethyl-4-aminopyridine (14.1 mg). Under an argon atmosphere, p-toluenesulfonyl chloride (263 mg) was added under ice cooling. After stirring at room temperature for 2 hours,

N,N-dimethyl-4-aminopyridine (141 mg) was added further and the resulting mixture was stirred at room temperature for 3 hours. After dilution with dichloromethane (20 ml), the reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate, water and saturated saline and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby the title compound (414 mg, 93%) was obtained.

[0684]

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 3.19(4H,br), 3.55(4H,br), 6.73(1H,d,J=15.6Hz), 7.40(1H,d,J=8.3Hz), 7.43(1H,d,J=15.6Hz), 7.76(1H,dd,J=8.3,2.5Hz), 8.50(1H,d,J=2.5Hz).

Elementary analysis for $C_{16}H_{22}ClN_3O_3S$

Calculated: C, 49.54; H, 5.72; N, 10.83; Cl, 9.14; S,8.27.

Found: C, 49.54; H, 5.73; N, 10.63; Cl, 9.44; S,8.15.

[0685]

[Referential Example 106]

1-(4-Bromo-2-methylbenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-bromo-2-methylbenzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0686]

^{1}H-NMR ($CDCl_3$) δ: 2.13(3H,s), 2.80-4.10(8H,m), 6.89(1H,d,J=8.3Hz), 7.30(1H,dd,J=8.3,2.0Hz), 7.35(1H,d,J=2.0Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.90-7.95(3H,m), 8.30(1H,br s).

MS (FAB) m/z: 507 [$(M+H)^+$, Br^{79}], 509 [$(M+H)^+$, Br^{81}].

[0687]

[Referential Example 107]

3-Methyl-4-(4-pyridyl)benzoic acid hydrochloride

In the same manner as in Referential Example 6, a reaction was conducted using 4-bromo-3-methylbenzoic acid as a raw material, whereby the title compound was obtained.

[0688]

^{1}H-NMR (DMSO-d_6) δ: 2.36(3H,s), 7.50(1H,d,J=7.8Hz), 7.92(1H,d,J=7.8Hz), 7.97(1H,s), 8.08(2H,d,J=6.4Hz), 8.99(2H,d,J=6.4Hz).

MS (FAB) m/z: 214 $(M+H)^+$.

[0689]

[Referential Example 108]

4-(2-Methyl-4-pyridyl)benzoic acid hydrochloride

In the same manner as in Referential Example 2, a reaction was conducted using 4-bromo-2-methylpyridine as a raw material, whereby the title compound was obtained.

[0690]

^{1}H-NMR (DMSO-d_6) δ: 2.81(3H,s), 8.10-8.16(4H,m),

8.23(1H,dd,J=6.4,1.5Hz), 8.36(1H,d,J=1.5Hz), 8.85(1H,d,J=6.4Hz).

MS (FAB) m/z: 214 $(M+H)^+$.

[0691]

[Referential Example 109]

1,4-Dibenzyl-2-methoxycarbonylmethylpiperazine

In toluene (250 ml), N,N'-dibenzylethylenediamine (12 ml) and triethylamine (12 ml) were dissolved, followed by the dropwise addition of methyl 3-bromocrotonate (7.0 ml) under ice cooling. The resulting mixture was stirred at room temperature for 24 hours. After the addition of triethylamine (2.0 ml), the resulting mixture was stirred at room temperature for 71 hours. The insoluble matter was filtered off and the filtrate was distilled under reduced pressure. The residue was added with 10% hydrochloric acid (300 ml) and crystals so precipitated were removed by filtration. Ethyl acetate was added to the filtrate. Potassium carbonate was added to the water layer so separated to make it alkaline. Ethyl acetate was added to the resulting mixture. The organic layer collected by separation was washed with saturated saline and dried over anhydrous potassium carbonate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (1.07 g, 62%) was obtained.

[0692]

^{1}H-NMR ($CDCl_3$) δ: 2.30-2.70(8H,m), 3.11(1H,br s), 3.40-

3.80(4H,m), 3.60(3H,s), 7.20-7.40(10H,m).

MS (FAB) m/z: 339 $(M+H)^+$.

[0693]

[Referential Example 110]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-methoxycarbonylmethylpiperazine

In acetic acid (40 ml), 1,4-dibenzyl-2-methoxycarbonylmethylpiperazine (2.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 2.00 g). The resulting mixture was subjected to catalytic reduction at room temperature for 4 hours under 4 atmospheric pressure. After removal of the catalyst by filtration, the residue obtained by distilling the filtrate under reduced pressure was added with dichloromethane and a saturated aqueous solution of sodium bicarbonate. The insoluble matter so precipitated was filtered off. The organic layer collected by separation was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in dichloromethane (30 ml), followed by the addition of 6-chloro-2-naphthylsulfonyl chloride (782 mg). The resulting mixture was stirred at 0°C for 2 hours. To the reaction mixture, triethylamine (410 µl) was added, followed by stirring at 0°C for further 3 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column

(dichloromethane ~ 3% methanol - dichloromethane), whereby the title compound (759 mg, 33%) was obtained.

[0694]

^{1}H-NMR ($CDCl_3$) δ: 1.71(1H,br s), 2.15-2.55(4H,m), 2.90-3.05(2H,m), 3.15-3.25(1H,m), 3.60-3.70(5H,m), 7.55-7.60(1H,m), 7.75-7.80(1H,m), 7.85-7.95(3H,m), 8.30(1H,s).

MS (FAB) m/z: 383 [$(M+H)^+$, Cl^{35}], 385 [$(M+H)^+$, Cl^{37}].

[0695]

[Referential Example 111]

4-tert-Butoxycarbonyl-1-[(3-chloro-1-propyl)sulfonyl]piperazine

Under an argon gas atmosphere, 1-tert-butoxycarbonylpiperazine (3.00 g) and triethylamine (2.24 ml) were dissolved in dichloromethane (40 ml) under ice cooling, followed by the addition of 3-chloro-1-propanesulfonic acid chloride (1.96 g). The resulting mixture was stirred for 20 minutes under ice cooling and then, at room temperature for 10 minutes. The reaction mixture was diluted with dichloromethane, washed with water and saturated saline and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and hexane, whereby the title compound (4.36 g, 83%) was obtained.

[0696]

^{1}H-NMR ($CDCl_3$) δ: 1.41(9H,s), 2.27-2.33(2H,m),

3.08(2H,t,J=7.3Hz), 3.26(4H,t,J=4.9Hz), 3.53(4H,t,J=4.9Hz), 3.69(2H,t,J=6.1Hz).

MS (FAB) m/z: 327 $(M+H)^+$

Elementary analysis for $C_{12}H_{23}ClN_2O_4S$

Calculated: C, 44.10; H, 7.09, Cl, 10.85; N, 8.57; S, 9.81.

Found: C, 44.18; H, 7.11; Cl, 10.69; N, 8.23; S, 9.76.

[0697]

[Referential Example 112]

4-tert-Butoxycarbonyl-1-[(3-hydroxy-1-propyl)sulfonyl]piperazine

In N,N-dimethylformamide (10 ml), 4-tert-butoxycarbonyl-1-[(3-chloro-1-propyl)sulfonyl]piperazine (1.18 g) was dissolved, followed by the addition of potassium acetate (1.06 g). After stirring at room temperature for 2 hours, the reaction mixture was stirred under heat at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate, followed by the addition of water and a saturated aqueous solution of sodium bicarbonate. After stirring, the organic layer collected by separation was washed with a 5% aqueous citric acid solution, water and saturated saline. After drying over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (20 ml). To the resulting solution, water and lithium hydroxide monohydrate (221 mg) were added, followed by stirring at room temperature for 18 hours. Ethyl acetate and saturated saline were added to the reaction mixture and the

organic layer was collected. From the water layer, an organic layer was extracted with ethyl acetate. The organic layers were combined together, washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate an hexane, whereby the title compound (944 mg, 84%) was obtained.

[0698]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.04-2.11(2H,m), 3.06(2H,t,J=7.6Hz), 3.25(4H,t,J=4.9Hz), 3.53(4H,t,J=4.9Hz), 3.80(2H,q,J=5.4Hz).

MS (FAB) m/z: 309 $(M+H)^+$.

Elementary analysis for $C_{12}H_{24}N_2O_5S$

Calculated: C, 46.74; H, 7.84; N, 9.08; S, 10.40.

Found: C, 46.80; H, 7.92; N, 9.05; S, 10.59.

[0699]

[Referential Example 113]

4-tert-Butoxycarbonyl-1-[(3-methoxymethyloxy-1-propyl)sulfonyl]piperazine

In dichloromethane (60 ml), 4-tert-butoxycarbonyl-1-[(3-hydroxy-1-propyl)sulfonyl]piperazine (3.00 g) was dissolved. To the resulting solution, diisopropylethylamine (2.72 ml) was added, followed by the addition of methoxymethyl chloride (1.11 ml) under ice cooling. After stirring at room temperature for 15 hours, the reaction mixture was diluted with dichloromethane, washed with water, a 5% aqueous citric acid

solution and saturated saline and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (3.32 g, 97%) was obtained.

[0700]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.06-2.13(2H,m), 3.03(2H,M), 3.25(4H,t,J=4.9Hz), 3.36(3H,s), 3.52(4H,t,J=4.9Hz), 3.63(2H,t,J=5.4Hz), 4.61(2H,s).

MS (FAB) m/z: 353 $(M+H)^+$.

Elementary analysis for $C_{14}H_{28}N_2O_6S$

Calculated: C, 47.71; H, 8.01; N, 7.95; S, 9.10.

Found: C, 47.77; H, 8.18; N, 7.97; S, 9.16.

[0701]

[Referential Example 114]

4-tert-Butoxycarbonyl-1-[(E)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-styrylsulfonyl]piperazine and 4-tert-butoxycarbonyl-1-[(Z)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-styrylsulfonyl]piperazine

Under an argon gas atmosphere, 4-tert-butoxycarbonyl-1-[3-methoxymethyloxy-1-propyl)sulfonyl]piperazine (800 mg) was dissolved in tetrahydrofuran (10 ml), followed by the dropwise addition of tert-butyl lithium (a 1.7M hexane solution, 1.47 ml) at -78°C. The resulting mixture was stirred at -78°C for one hour. After the addition of trimethylsilyl chloride

(0.317 ml) and stirring at -78°C for 90 minutes, tert-butyl lithium (a 1.7M hexane solution, 1.47 ml) was added dropwise to the reaction mixture and stirring was effected at -78°C for 90 minutes. At -78°C, a solution of p-chlorobenzaldehyde (352 mg) in tetrahydrofuran (tetrahydrofuran: 8 ml) was added dropwise to the reaction mixture. After stirring for 2 hours, the temperature of the reaction mixture was allowed to rise back to room temperature over 15 hours, at which temperature it was stirred for 6 hours. Under ice cooling, a 5% citric acid solution (20 ml) and ethyl acetate (150 ml) were added to the reaction mixture. The organic layer collected by separation was washed with water and saturated saline and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 ~ 2:1), whereby the title compound was obtained as an E-form (307 mg, 28%) and Z-form (751 mg, 70%).

[0702]

E form:

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 2.87(2H,t,J=7.3Hz), 3.21-3.28(4H,m), 3.35(3H,s), 3.46-3.56(4H,m), 3.80(2H,t,J=7.3Hz), 4.60(2H,s), 7.40(2H,d,J=8.5Hz), 7.46(2H,d,J=8.5Hz), 7.54(1H,s).

[0703]

Z-form:

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 2.77(2H,dt,J=6.4,1.0Hz), 2.91-2.98(4H,m), 3.19-3.25(4H,m), 3.38(3H,s), 3.82(2H,t,J=6.4Hz), 4.66(2H,s), 7.07(1H,s), 7.32(2H,d,J=8.6Hz), 7.35(2H,d,J=8.6Hz).

[0704]

[Referential Example 115]

1-Benzenesulfonyl-6-chloroindole

At -78°C, n-butyl lithium (a 1.61M hexane solution, 3.34 ml) was added to a solution of 6-chloroindole (777 mg) in tetrahydrofuran (25 ml), followed by heating to -40°C over 1 hour. The reaction mixture was cooled back to -78°C and added with benzenesulfonyl chloride (867 µl). The resulting mixture was heated to room temperature over 3 hours. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (40 g of silica gel, hexane : ethyl acetate = 5:7). The white solid so obtained was recrystallized from ethanol, whereby the title compound (826 mg, 55%) was obtained as a white solid.

[0705]

^{1}H-NMR ($CDCl_3$) δ: 6.64(1H,d,J=3.9Hz), 7.21(1H,dd,J=8.3,1.2Hz), 7.42-7.60(5H,m), 7.88(2H,d,J=7.3Hz), 8.03(1H,s).

Elementary analysis for $C_{14}H_{10}ClNO_2S$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80;

S, 10.99.

Found: C, 57.48; H, 3.75; Cl, 12.34; N, 4.87;

S, 10.87.

[0706]

In the same manner as in Referential Example 115, the compounds which will described below in Referential Examples 116 and 117 were synthesized.

[0707]

[Referential Example 116]

1-Benzenesulfonyl-5-chloroindole

^{1}H-NMR ($CDCl_3$) δ: 6.61(1H,d,J=3.9Hz), 7.26(1H,dd,J=8.3,2.0Hz), 7.45(2H,t,J=7.3Hz), 7.50(1H,d,J=2.0Hz), 7.56(1H,m), 7.59(1H,d,J=3.9Hz), 7.86(2H,m), 7.92(1H,d,J=8.3Hz).

Elementary analysis for $C_{14}H_{10}ClNO_2S$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80;

S, 10.99.

Found: C, 57.82; H, 3.58; Cl, 11.91; N, 4.79;

S, 10.92.

[0708]

[Referential Example 117]

1-Benzenesulfonyl-5-bromoindole

^{1}H-NMR ($CDCl_3$) δ: 6.60(1H,d,J=3.7Hz), 7.42(1H,dd,J=8.8,2.0Hz), 7.45(2H,t,J=8.8Hz), 7.55(1H,d,J=8.8Hz), 7.57(1H,d,J=3.7Hz), 7.73(1H,d,J=2.0Hz), 7.86(2H,d,J=8.8Hz),

7.87(1H,d,J=1H,d,J=8.8Hz).

Elementary analysis for $C_{14}H_{10}BrNO_2S$

Calculated: C, 50.01; H, 3.00; N, 4.17; Br, 23.77; S, 9.54.

Found: C, 49.96; H, 2.97; N, 4.02; Br, 23.90; S, 9.53.

[0709]

[Referential Example 118]

1-Benzenesulfonyl-5-trimethylsilylethynylindole

In tetrahydrofuran (7.00 ml), 1-benzenesulfonyl-5-bromoindole (1.50 g) and triphenylphosphine (351 mg) were dissolved. Triethylamine (20 ml), N,N-dimethylformamide (7.00 ml), trimethylsilylacetylene (945 µl) and palladium acetate (100 mg) were added to the resulting solution at room temperature, followed by heating under reflux for 5 hours. After the reaction mixture was allowed to cool down to room temperature, ethyl acetate and water were added to the reaction mixture and the organic layer was collected by separation. The resulting organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 20:1 to 10:1), whereby the title compound (935 mg, 59%) was obtained as a white solid.

[0710]

^{1}H-NMR ($CDCl_3$) δ: 0.24(9H,s), 6.62(1H,d,J=3.9Hz), 7.42(1H,dd,J=8.8,1.5Hz), 7.44(2H,t,J=7.8Hz), 7.52(1H,d,J=7.8Hz), 7.56(1H,d,J=3.9Hz), 7.66(1H,d,J=1.5Hz), 7.85(2H,d,J=7.8Hz), 7.92(1H,d,J=8.8Hz).

MS (FAB) m/z: 354 $(M+H)^+$

[0711]

[Referential Example 119]

5-Chloro-1-ethylindole

In benzene (10 ml), 5-chloroindole (1.52 g) was dissolved, followed by the addition of a 50% aqueous solution of sodium hydroxide (10 ml), tetrabutylammonium bromide (161 mg) and bromoethane (1.64 g). The resulting mixture was stirred at room temperature for 40 hours. After the addition of a saturated aqueous solution of ammonium chloride to the reaction mixture, water and dichloromethane were added and the organic layer was collected. After the resulting organic layer was dried over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:20), whereby the title compound (1.68 g, 93%) was obtained as colorless crystals.

[0712]

^{1}H-NMR ($CDCl_3$) δ: 1.46(3H,t,J=7.3Hz), 4.16(2H,q,J=7.3Hz), 6.43(1H,d,J=2.4Hz), 7.14(1H,d,J=2.4Hz), 7.15(1H,d,J=8.3Hz), 7.26(1H,J=8.3Hz), 7.59(1H,s).

MS (EI) m/z: 179 (M^+, Cl^{35}), 181 (M^+, Cl^{37}).

[0713]

[Referential Example 120]

1-Benzenesulfonyl-6-chloroindole-2-sulfonyl chloride

After the dropwise addition of tert-butyl lithium (a 1.56M pentane solution, 1.78 ml) to a solution of 1-benzenesulfonyl-6-chloroindole (777 mg) in ether (12 ml) at -78°C, the mixture was heated to 0°C over 30 minutes. The reaction mixture was stirred for 1 hour and then cooled back to -78°C. A sulfurous acid gas was then introduced into the reaction mixture. After heating to room temperature over 1 hour, stirring was conducted for 1 hour. The reaction mixture was concentrated under reduced pressure. Hexane was added to the concentrate, followed by concentration under reduced pressure again. The residue was dissolved in dichloromethane. To the resulting solution, N-chlorosuccinimide (390 mg) was added at 0°C, followed by heating over 1 hour to room temperature. Stirring was then conducted for 30 minutes. Dichloromethane and water were added to the reaction mixture cause separation. The organic layer thus obtained was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was recrystallized from methanol, whereby the title compound (857 mg, 79%) was obtained as a white solid.

[0714]

^{1}H-NMR ($CDCl_3$) δ: 7.39(1H,dd,J=8.3,1.6Hz), 7.48-7.67(4H,m), 7.68(1H,s), 8.08(2H,d,J=7.3Hz), 8.35(1H,s).

Elementary analysis for $C_{14}H_9ClNO_4S_2$

Calculated: C, 43.09; H, 2.32; Cl, 18.17; N, 3.59; S, 16.43.

Found: C, 43.32; H, 2.67; Cl, 18.25; N, 3.64; S, 16.22.

[0715]

In the same manner as in Referential Example 120, compounds which will be described below in Referential Examples 121 to 128 were synthesized.

[0716]

[Referential Example 121]

1-Benzenesulfonylindole-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.40(1H,t,J=7.6Hz), 7.45-7.53(2H,m), 7.57-7.67(2H,m), 7.69(1H,d,J=7.8Hz), 7.73(1H,s), 8.08(2H,d,J=7.3Hz), 8.31(1H,d,J=8.8Hz).

MS (EI) m/z: 355M$^+$.

Elementary analysis for $C_{14}H_{10}ClNO_4S_2$

Calculated: C, 47.26; H, 2.83; Cl, 9.96; N, 3.94; S, 18.02.

Found: C, 47.33; H, 3.08; Cl, 10.04; N, 3.98; S, 18.18.

[0717]

[Referential Example 122]

1-Benzenesulfonyl-5-chloroindole-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.46-7.54(2H,m), 7.58(1H,dd,J=9.3,2.0Hz), 7.63(1H,t,J=7.3Hz), 7.64(1H,s), 7.67(1H,d,J=2.0Hz), 8.06(2H,d,J=7.3Hz), 8.26(1H,d,J=9.3Hz).

MS (EI) m/z: 291 (M$^+$, Cl^{35}), 293 (M$^+$, Cl^{37}).

Elementary analysis for $C_{14}H_9Cl_2NO_4S_2$

Calculated: C, 43.09; H, 2.32; Cl, 18.27; N, 3.59; S, 16.43.

Found: C, 42.98; H, 2.51; Cl, 18.36; N, 3.59 S, 16.47.

[0718]

[Referential Example 123]

5-Chloro-1-ethylindole-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.52(3H,t,J=7.3Hz), 4.59(2H,q,J=7.3Hz), 7.36(1H,s), 7.39(1H,d,J=8.8Hz), 7.45(1H,dd,J=8.8,2.0Hz), 7.73(1H,d,J=2.0Hz).

MS (EI) m/z: 277 [M^+, Cl^{35}], 279 [M^+, Cl^{37}]

[0719]

[Referential Example 124]

1-Benzenesulfonyl-5-trimethylsilylethynylindole-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 0.26(9H,s), 7.48(2H,t,J=7.8Hz), 6.61(1H,t,J=7.8Hz), 7.65(1H,s), 7.69(1H,dd,J=8.8,1.5Hz), 7.79(1H,d,J=1.5Hz), 8.04(2H,d,J=7.8Hz), 8.24(1H,d,J=8.8Hz).

MS (FAB) m/z: 452 [$(M+H)^+$, Cl^{35}], 454 [$(M+H)^+$, Cl^{37}]

[0720]

[Referential Example 125]

5-Chlorobenzo[b]furan-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.57(1H,dd,J=8.8,2.0Hz), 7.59(1H,s), 7.61(1H,d,J=8.8Hz), 7.76(1H,d,J=2.0Hz).

MS (EI) m/z: 250 (M^+, Cl^{35}), 252 (M^+, Cl^{37}).

Elementary analysis for $C_8H_4Cl_2O_3S$

Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.33; H, 1.71; Cl, 28.16; S, 12.57.

[0721]

[Referential Example 126]

6-Chlorobenzo[b]furan-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.43(1H,dd,J=8.8,2.0Hz), 7.62(1H,s), 7.69(1H,s), 7.70(1H,d,J=8.8Hz).

MS (EI) m/z: 250 (M^+, Cl^{35}), 252 (M^+, Cl^{37}).

Elementary analysis for $C_8H_4Cl_2O_3S$

Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.31; H, 1.60; Cl, 28.34; S, 12.60.

[0722]

[Referential Example 127]

5-Chlorobenzo[b]thiophene-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.57(1H,dd,J=8.8,2.0Hz), 7.85(1H,d,J=8.8Hz), 7.96(1H,d,J=2.0Hz), 8.08(1H,s).

MS (FD) m/z: 266 (M^+, Cl^{35}), 268 (M^+, Cl^{37}).

[0723]

[Referential Example 128]

6-Chlorobenzo[b]thiophene-2-sulfonyl chloride

^{1}H-NMR ($CDCl_3$) δ: 7.51(1H,dd,J=8.3,1.5Hz), 7.90(1H,d,J=8.3Hz), 7.92(1H,s), 8.11(1H,s).

MS (FAB) m/z: 266 [$(M+H)^+$, Cl^{35}], 268 [$(M+H)^+$, Cl^{37})].

[0724]

[Referential Example 129]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

To a solution of 1-benzenesulfonyl-5-chloroindole-2-sulfonyl chloride (4.41 g) in dichloromethane (75 ml),

tert-butyl-1-piperazine carboxylate (2.21 g) and triethylamine (1.65 ml) were added under ice cooling. The resulting mixture was stirred at room temperature for 3 hours. After completion of the reaction, water and dichloromethane were added to the reaction mixture. The organic layer obtained by separation was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : n-hexane = 1:20), whereby the title compound (3.63 g, 60%) was obtained as colorless crystals.

[0725]

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 3.35-3.42(4H,br), 3.50-3.55(4H,br), 7.40-7.48(4H,m), 7.53-7.58(2H,m), 8.00-8.05(2H,m), 8.23(1H,d,J=8.8Hz).

[0726]

In the same manner as in Referential Example 129, compounds which will described below in Referential Examples 130 to 133 were synthesized.

[0727]

[Referential Example 130]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonylindol-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 3.34-3.44(4H,br), 3.48-3.56(4H,br), 7.33(1H,t,J=7.3Hz), 7.36-7.45(2H,m), 7.47-7.61(4H,m), 8.04(2H,d,J=7.3Hz), 8.29(1H,d,J=8.8Hz).

MS (EI) m/z: 505M^+.

[0728]

[Referential Example 131]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethylindol-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 1.41(3H,t,J=7.3Hz), 1.43(9H,s), 3.16-3.23(4H,m), 3.48-3.55(4H,m), 4.45(2H,q,J=7.3Hz), 7.03(1H,s), 7.32-7.34(2H,m), 7.66(1H,d,J=2.0Hz).

MS (EI) m/z: 427 (M^+, Cl^{35}), 429 (M^+, Cl^{37}).

[0729]

[Referential Example 132]

1-tert-Butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]homopiperazine

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.98-2.17(2H,m), 3.42-3.57(8H,m), 7.28(1H,s), 7.41-7.46(3H,m), 7.53-7.57(2H,m), 8.05(2H,d,J=7.3Hz), 8.20(1H,d,J=9.3Hz).

MS (FAB) m/z: 554 [$(M+H)^+$, Cl^{35}], 556 [$(M+H)^+$, Cl^{37}].

[0730]

[Referential Example 133]

cis-1-[(1-Benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-3,5-dimethylpiperazine

^{1}H-NMR ($CDCl_3$) δ: 1.07(6H,d,J=6.4Hz), 2.45-2.55(2H,m), 2.95-3.05(2H,m), 3.75-3.80(2H,m), 7.35-7.50(4H,m), 7.50-7.60(2H,m), 8.00-8.05(2H,m), 8.22(1H,d,J=9.3Hz).

MS (FAB) m/z: 468 [$(M+H)^+$, Cl^{35}], 470 [$(M+H)^+$, Cl^{37}].

[0731]

[Referential Example 134]

3-Ethoxycarbonyl-1-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

A saturated ethanol hydrochloride solution was added to tert-butyl-1-(3-ethoxycarbonyl)piperazinecarboxylate (3.97 g) and the mixture was stirred for 30 minutes. After the solvent was distilled off under reduced pressure, the residue was suspended in dichloromethane (200 ml). To the resulting suspension, 1-benzenesulfonyl-5-chloroindole-2-sulfonyl chloride (6.00 g) and triethylamine (6.40 ml) were added, followed by stirring at room temperature for 3 hours. Water and dichloromethane were added to the reaction mixture. The organic layer collected by separation was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:20), whereby the title compound (4.44 g, 56%) was obtained as white crystals.

[0732]

^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t,J=6.8Hz), 2.87-2.95(1H,m), 3.11-3.28(3H,m), 3.57-3.66(2H,m), 3.91-3.98(1H,m), 4.17(2H,q,J=6.8Hz), 7.38-7.48(4H,m), 7.55-7.59(2H,m), 8.03(2H,d,J=7.8Hz), 8.21(1H,d,J=9.3Hz).

MS (EI) m/z: 511 (M^+, Cl^{35}), 513 (M^+, Cl^{37})+.

[0733]

[Referential Example 135]

1-tert-Butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

To 1-tert-butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine (4.84 g), a 0.5N methanol solution (20 ml) of sodium hydroxide was added, followed by stirring at room temperature for 1 hour. Under ice cooling, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. Water and dichloromethane were then added and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:20), whereby the title compound (3.33 g, 93%) was obtained as colorless powder.

[0734]

^{1}H-NMR ($CDCl_3$) δ: 1.40(9H,s), 3.05-3.14(4H,m), 3.48-3.57(4H,m), 6.96(1H,d,J=2.0Hz), 7.33(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.67(1H,d,J=2.0Hz), 8.78(1H,br).

MS (FAB) m/z: 400 [$(M+H)^+$, Cl^{35}], 402 [$(M+H)^+$, Cl^{37}].

[0735]

In the same manner as in Referential Example 135, the compound shown in Referential Example 136 was synthesized.

[0736]

[Referential Example 136]

1-[(5-Chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine

^{1}H-NMR ($CDCl_3$) δ: 2.70-2.82(1H,m), 2.84-2.97(2H,m), 3.06-3.16(1H,m), 3.37-3.46(1H,m), 3.61(1H,dd,J=8.3,3.4Hz), 3.69-3.80(1H,m), 3.75(3H,s), 6.98(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.67(1H,s), 8.80(1H,s).

MS (EI) m/z: 357 (M^+, Cl^{35}), 359 (M^+, Cl^{37})$^+$.

[0737]

[Referential Example 137]

3-(N-Methylcarbamoyl)-1-[(5-chloroindol-2-yl)sulfonyl]piperazine

In tetrahydrofuran (25 ml), 1-[(5-chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine (480 mg) was dissolved. After a 0.2N methanol solution (7 ml) of sodium hydroxide and water (2 ml) were added to the resulting solution and the mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. The resulting yellow amorphous substance (520 mg) was dissolved in N,N-dimethylformamide (60 ml). At room temperature, 1-hydroxybenzotriazole (18.1 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (334 mg), methylamine hydrochloride (90.5 mg) and N-methylmorpholine (271 mg) were added to the resulting solution, followed by stirring at room temperature for 12 hours. The solvent was then distilled off under reduced pressure. Water and ethyl acetate were added to the residue and the organic layer was collected. The resulting

organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the title compound (140 mg, 29%) was obtained as a brown amorphous solid.

[0738]

^{1}H-NMR (DMSO-d_6) δ: 2.39-2.52(2H,m), 2.64(3H,d,J=3.9Hz), 2.18-2.30(1H,m), 2.94-3.00(1H,m), 3.20-3.37(2H,m), 3.57-3.66(1H,m), 6.90-6.95(1H,br), 7.22-7.27(1H,br), 7.44-7.49(1H,m), 7.66-7.78(2H,m), 8.04-8.17(3H,m), 12.24(1H,m).

[0739]

[Referential Example 138]

1-[(5-Chloroindol-2-yl)sulfonyl]piperazine

In methanol (100 ml), 1-tert-butoxycarbonyl-4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine (3.63 g) was dissolved. Under ice cooling, a 0.2N methanol solution (100 ml) of sodium hydroxide was added to the resulting solution, followed by stirring at room temperature for 12 hours. After a saturated aqueous solution of ammonium chloride was added to the reaction mixture under ice cooling, water and dichloromethane were added and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. After the solid so precipitated was collected by filtration, it was dissolved in saturated ethanol hydrochloride, followed by stirring for 30 minutes. The reaction mixture was distilled

under reduced pressure to remove the solvent, followed by drying under reduced pressure, whereby the title compound (1.25 g, 54%) was obtained as colorless powder.

[0740]

^{1}H-NMR (DMSO-d_6) δ: 3.25-3.43(8H,br), 7.46(1H,d,J=8.8Hz), 7.64(1H,d,J=8.8Hz), 7.93(1H,s), 9.33(1H,br), 12.70(1H,br).

MS (EI) m/z: 298 (M^+, Cl^{35}), 300 (M^+, Cl^{37}).

Elementary analysis for $C_{12}H_{14}ClN_3O_2S \cdot HCl \cdot 0.5H_2O$

Calculated: C, 41.75; H, 4.67; Cl, 20.54; N, 12.17; S, 9.29.

Found: C, 41.78; H, 4.98; Cl, 20.40; N, 11.88; S, 9.34.

[0741]

[Referential Example 139]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-methylindol-2-yl)sulfonyl]piperazine

Sodium hydride (about 60% in oil, 50.3 mg) washed twice with petroleum ether was suspended in tetrahydrofuran (10 ml), followed by the addition of a solution of 1-tert-butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (457 mg) in tetrahydrofuran (tetrahydrofuran: 10 ml) under ice cooling. The resulting mixture was stirred for 30 minutes. Under ice cooling, iodomethane (179 mg) was added to the reaction mixture. The resulting mixture was heated to room temperature and stirred for 85 hours. Water and diethyl ether were added and the organic layer was collected. The resulting organic

layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the title compound (270 mg, 57%) was obtained as colorless powder.

[0742]

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 3.14-3.21(4H,m), 3.48-3.55(4H,m), 3.96(3H,s), 7.06(1H,s), 7.31(1H,d,J=9.3Hz), 7.36(1H,d,J=9.3,2.0Hz), 7.66(1H,d,J=2.0Hz).

MS (FAB) m/z: 413 [$(M+H)^+$, Cl^{35}], 415 [$(M+H)^+$, Cl^{37}].

[0743]

In the same manner as in Example 139, the compound shown in Referential Example 140 was synthesized.

[0744]

[Referential Example 140]

1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.3Hz), 1.43(9H,s), 3.10-3.19(4H,m), 3.45-3.53(4H,m), 4.22(2H,q,J=7.3Hz), 5.15(2H,s), 7.15(1H,s), 7.17(1H,d,J=8.8Hz), 7.26(1H,s), 7.36(1H,dd,J=8.8,2.0Hz), 7.68(1H,d,J=2.0Hz).

MS (FAB) m/z: 485 [$(M+H)^+$, Cl^{35}], 487 [$(M+H)^+$, Cl^{37}].

[0745]

[Referential Example 141]

cis-4-[(1-Benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-1-

(4-bromobenzoyl)-2,6-dimethylpiperazine

In dichloromethane (40 ml), cis-1-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-3,5-dimethylpiperazine (1.30 g) was dissolved. To the resulting solution, diisopropylethylamine (645 µl) was added under ice cooling, followed by the dropwise addition of a solution of 4-bromobenzoyl chloride (0.74 g) in dichloromethane (dichloromethane: 5 ml). Stirring was then effected at room temperature for 3 hours. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture. The organic layer collected by separation was washed with 0.5N hydrochloric acid and saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1 to 1:1), whereby the title compound (1.8 g, 97%) was obtained as a pale yellow amorphous.

[0746]

^{1}H-NMR ($CDCl_3$) δ: 1.45(6H,d,J=6.8Hz), 3.05-3.15(2H,m), 3.74(2H,m), 4.40(2H,br), 7.23(2H,d,J=8.8Hz), 7.40-7.50(4H,m), 7.50-7.60(4H,m), 8.00-8.05(2H,m), 8.24(1H,d,J=9.3Hz).

MS (EI) m/z: 649 [$(M+H)^+$, Cl^{35}], 651 [$(M+H)^+$, Cl^{37}].

[0747]

[Referential Example 142]

Ethyl 2-(4-pyridyl)-5-pyrimidinecarboxylate

Sodium ethoxide (590 mg) was dissolved in anhydrous ethanol (50 ml) at room temperature. To the resulting solution,

4-amidinopyridine hydrochloride (1.31 g) was added, followed by the dropwise addition of a solution of ethyl 2,2-diformylacetate (1.20 g) in anhydrous ethanol (ethanol: 50 ml). The resulting mixture was heated under reflux for 6 hours. To the residue obtained by distilling off the solvent under reduced pressure, dichloromethane and water were added. The organic layer collected by separation was dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, the residue was crystallized in ethanol, whereby the title compound (279 mg, 15%) was obtained as colorless crystals.

[0748]

^{1}H-NMR (DMSO-d_6) δ: 1.46(3H,t,J=7.3Hz), 4.48(2H,q,J=7.3Hz), 8.35(2H,d,J=5.9Hz), 8.82(2H,d,J=5.9Hz), 9.38(2H,s).

MS (FAB) m/z: 230 $(M+H)^+$.

Elementary analysis for $C_{12}H_{11}N_3O_2$

Calculated: C, 62.87; H, 4.84; N, 18.33.

Found: C, 62.80; H, 4.78; N, 18.25.

[0749]

[Referential Example 143]

2-(4-Pyridyl)-5-pyridiminecarboxylic acid

In the same manner as in Referential Example 11, a reaction was effected using ethyl 2-(4-pyridyl)-5-pyrimidinecarboxylic acid instead as a raw material, whereby the title compound was obtained.

[0750]

^{1}H-NMR (DMSO-d_6) δ: 8.32(2H,d,J=5.9Hz), 8.82(2H,d,J=5.9Hz), 9.38(2H,s).

MS (FAB) m/z: 201 M^+.

Elementary analysis for $C_{10}H_7N_3O_2 \cdot 0.1H_2O$

Calculated: C, 59.17; H, 3.58; N, 20.70.

Found: C, 59.09; H, 3.49; N, 20.69.

[0751]

[Referential Example 144]

1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was effected using 5-bromo-2-pyrimidinecarboxylic acid and 1-[(5-chloroindol-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained as a colorless solid.

[0752]

^{1}H-NMR ($CDCl_3$) δ: 3.14-3.17(2H,m), 3.25-3.29(2H,m), 3.52-3.55(2H,m), 3.92-3.95(2H,m), 7.97(1H,s), 7.32-7.40(2H,m), 7.69(1H,s), 8.79(1H,br,s), 8.84(2H,s).

MS (FAB) m/z: 484 [$(M+H)^+$, Cl^{35} and Br^{79}], 486 [$(M+H)^+$, Cl^{35} and Br^{81}, Cl^{37} and Br^{79}], 488 [$(M+H)^+$, Cl^{37} and Br^{81}].

[0753]

[Referential Example 145] 6-Chloro-2-mercaptobenzothiazole

Under ice cooling, a solution of p-chloroaniline (5.70 g) in acetic acid (acetic acid: 7 ml) was added dropwise over 30

minutes to disulfur dichloride (25.0 ml) over 30 minutes, followed by stirring at room temperature for 3 hours and then at about 80°C for 3 hours. Benzene (50 ml) was added to the reaction mixture. The green crystals were collected by filtration and washed with benzene. The resulting crystals were dissolved in ice water (500 ml) and the solution was stirred for 1 hour. To the reaction mixture, a 6N aqueous solution of sodium hydroxide was added to make the mixture alkaline. Sodium bicarbonate (6 g) was then added and the mixture was stirred at 100°C for 1 hour. Activated carbon was added to the reaction mixture, followed by Celite filtration. To the filtrate, carbon disulfide (2.70 ml) was added, followed by heating to about 50°C. Stirring was then conducted for 1.5 hours. After cooling to room temperature, the reaction mixture was made acidic with 1N hydrochloric acid. Colorless powder thus precipitated was collected by filtration and dried, whereby the title compound (1.30 g, 14%) was obtained.

[0754]

^{1}H-NMR (DMSO-d_6) δ: 7.28(1H,d,J=8.3Hz), 7.45(1H,dd,J=8.3,2.0Hz), 7.86(1H,d,J=2.0Hz).

MS (FAB) m/z: 202 [$(M+H)^+$, Cl^{35}], 204 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_7H_4ClNS_2$

Calculated: C, 41.68; H, 2.00; Cl, 17.58; N, 6.94; S, 31.80.

Found: C, 41.64; H, 2.13; Cl, 17.83; N, 6.94; S, 31.70.

[0755]

[Referential Example 146]

1-tert-Butoxycarbonyl-4-[(5-chloroenzothiazol-2-yl)sulphenyl]piperazine

At room temperature, tert-butyl-1-piperazine carboxylate (5.58 g), 5-chloro-2-mercaptobenzothiazole (1.21 g) and sodium hydroxide (0.48 g) were dissolved in water (25 ml), followed by the dropwise addition of an aqueous solution (25 ml) containing iodine (1.53 g) and potassium iodide (1.65 g). The colorless crystals so precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (1.1 g, 48%) was obtained.

[0756]

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 3.24(4H,br), 3.58(4H,br s), 7.26(1H,m), 7.70(1H,d,J=8.3Hz), 7.81(1H,s).

MS (FAB) m/z: 386 [$(M+H)^+$, Cl^{35}], 388 [$(M+H)^+$, Cl^{37}].

[0757]

In the same manner as in Referential Example 146, the compound shown in Referential Example 147 was synthesized.

[0758]

[Referential Example 147]

1-tert-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulphenyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 3.24(4H,br s), 3.58(4H,br s), 7.37(1H,dd,J=8.8,2.0Hz), 7.73(1H,d,J=8.8Hz), 7.77(1H,d,J=2.0Hz).

MS (FAB) m/z: 386 [$(M+H)^+$, Cl^{35}], 388 [$(M+H)^+$, Cl^{37}].

[0759]

[Referential Example 148]

1-tert-Butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine

At room temperature, 1-tert-butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulphenyl]piperazine (1.10 g) and potassium carbonate (1.30 g) were suspended in a mixed solvent of ethanol (30 ml) and water (10 ml), followed by the dropwise addition of a solution of 3-chloroperbenzoic acid (2.11 g) in ethanol (25 ml) at 0°C. The reaction mixture was heated to room temperature and stirred for 24 hours. Sodium thiosulfate and ethyl acetate were added and the organic layer was collected. The organic layer thus obtained was dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby the title compound (293 mg, 25%) was obtained.

[0760]

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 3.35-3.43(4H,m), 3.51-3.58(4H,m), 7.55(1H,dd,J=8.8,1.5Hz), 7.90(1H,d,J=8.8Hz), 8.18(1H,d,J=1.5Hz).

MS (FAB) m/z: 418 [$(M+H)^+$, Cl^{35}], 420 [$(M+H)^+$, Cl^{37}].

[0761]

In the same manner as in Referential Example 148, the

compound shown in Referential Example 149 was synthesized.

[0762]

[Referential Example 149]

1-tert-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 3.35-3.43(4H,m), 3.50-3.58(4H,m), 7.59(1H,dd,J=8.8,2.0Hz), 7.97(1H,d,J=2.0Hz), 8.10(1H,d,J=8.8Hz).

MS (FAB) m/z: 418 [$(M+H)^+$, Cl^{35}], 420 [$(M+H)^+$, Cl^{37}].

[0763]

In the same manner as in Referential Example 35, compounds shown in Referential Examples 150 and 151 were synthesized, respectively.

[0764]

[Referential Example 150]

1-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazine hydrochloride

^{1}H-NMR (DMSO-d_6) δ: 3.23(4H,br s), 3.56(4H,br s), 7.78(1H,dd,J=8.8,2.0Hz), 8.39-8.43(2H,m).

MS (FAB) m/z: 318 [$(M+H)^+$, Cl^{35}], 320 [$(M+H)^+$, Cl^{37}].

[0765]

[Referential Example 151]

1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazine hydrochloride

^{1}H-NMR (DMSO-d_6) δ: 3.21-3.27(4H,m), 3.52-3.57(4H,m),

7.79(1H,dd,J=8.8,2.0Hz), 8.28(1H,d,J=8.8Hz),

8.53(1H,d,J=2.0Hz).

MS (FAB) m/z: 318 [$(M+H)^+$, Cl^{35}], 320 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{11}H_{12}ClN_3O_2S_2 \cdot 1.05HCl \cdot 0.5H_2O$

Calculated: C, 36.19; H, 3.88; Cl, 19.91; N, 11.51;

S, 17.57.

Found: C, 36.19; H, 4.10; Cl, 20.08; N, 11.50;

S, 17.19.

[0766]

In the same manner as in Referential Example 1, compounds shown in Referential Examples 152 to 155 were synthesized, respectively.

[0767]

[Referential Example 152]

1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine

^{1}H-NMR (DMSO-d_6) δ: 3.20(4H,br), 3.45(4H,br),

7.62(1H,d,J=8.8Hz), 7.76(1H,s), 7.85(1H,d,J=8.8Hz),

7.96(1H,s), 9.41(1H,br).

MS (FAB) m/z: 301 [$(M+H)^+$, Cl^{35}], 303 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{12}H_{13}ClN_2O_3S \cdot HCl \cdot 0.1H_2O$

Calculated: C, 42.51; H, 4.22; Cl, 20.91; N, 8.26; S, 9.46.

Found: C, 42.38; H, 4.33; Cl, 20.92; N, 8.18; S, 9.58.

[0768]

[Referential Example 153]

1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine

^{1}H-NMR (DMSO-d_6) δ: 3.20(4H,t,J=4.9Hz), 3.42(4H,t,J=4.9Hz), 7.51(1H,d,J=7.8Hz), 7.82(1H,s), 7.89(1H,d,J=7.8Hz), 9.18(1H,br).

MS (FAB) m/z: 301 [$(M+H)^+$, Cl^{35}], 303 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{12}H_{13}ClN_2O_3S \cdot HCl \cdot 0.5H_2O$

Calculated: C, 41.63; H, 4.37; Cl, 20.48; N, 8.09; S, 9.26.

Found: C, 41.54; H, 4.32; Cl, 20.49; N, 7.90; S, 9.07.

[0769]

[Referential Example 154]

1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.50(8H,m), 7.64(1H,dd,J=8.8,2.0Hz), 8.12(1H,s), 8.20(1H,s), 8.23(1H,d,J=8.8Hz), 9.22(2H,br s).

MS (FAB) m/z: 317 [$(M+H)^+$, Cl^{35}], 319 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{12}H_{13}ClN_2O_2S_2 \cdot HCl \cdot 1.6H_2O$

Calculated: C, 37.72; H, 4.54; Cl, 18.56; N, 7.33; S, 16.78.

Found: C, 37.56; H, 4.67; Cl, 18.72; N, 7.17; S, 16.56.

[0770]

[Referential Example 155]

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.38(8H,m), 7.59(1H,dd,J=8.8,2.0Hz), 8.10(1H,d,J=8.8Hz), 8.16(1H,s), 8.36(1H,d,J=8.8Hz), 9.29(2H,br s).

MS (FAB) m/z: 317 [$(M+H)^+$, Cl^{35}], 319 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{12}H_{13}ClN_2O_2S_2 \cdot HCl$

Calculated: C, 40.80; H, 3.99; Cl, 20.07; N, 7.93; S, 18.15.

Found: C, 40.64; H, 4.04; Cl, 20.06; N, 7.90; S, 17.91.

[0771]

[Referential Example 156]

1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

[0772]

^{1}H-NMR ($CDCl_3$) δ: 3.10-3.13(2H,m), 3.22-3.25(2H,m), 3.49-3.53(2H,m), 3.90-3.94(2H,m), 7.59(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,1.5Hz), 7.91-7.95(3H,m), 8.30(1H,br s), 8.82(2H,s).

MS (FAB) m/z: 495 [$(M+H)^+$, Cl^{35} and Br^{79}], 497 [$(M+H)^+$, Cl^{35} and Br^{81}, Cl^{37} and Br^{79}], 499 [$(M+H)^+$, Cl^{37} and Br^{81}].

[0773]

[Referential Example 157]

1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(6-chlorobenzothiophen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

[0774]

^{1}H-NMR ($CDCl_3$) δ: 3.19-3.23(2H,m), 3.29-3.33(2H,m), 3.53-

3.56(2H,m), 3.93-3.97(2H,m), 7.46(1H,dd,J=8.8,1.5Hz), 7.77(1H,s), 7.83(1H,d,J=8.8Hz), 7.88(1H,d,J=1.5Hz), 8.84(2H,s).

MS (FAB) m/z: 501 [$(M+H)^+$, Cl^{35} and Br^{79}], 503 [$(M+H)^+$, Cl^{35} and Br^{81}, Cl^{37} and Br^{79}], 505 [$(M+H)^+$, Cl^{37} and Br^{81}].

Elementary analysis for $C_{17}H_{14}BrClN_4O_3S_2$

Calculated: C, 40.69; H, 2.81; N, 11.17; S, 12.78.

Found: C, 40.90; H, 2.87; N, 10.92; S, 12.87.

[0775]

[Referential Example 158]

1-Benzyl-4-tert-butoxycarbonylpiperazine

In acetonitrile (80 ml), tert-butyl-1-piperazine carboxylate (2.50 g) was dissolved. Under ice cooling, benzyl bromide (1.59 ml) and triethylamine (1.87 ml) were added dropwise to the resulting solution, followed by stirring at room temperature for 90 minutes. After the solvent was distilled off under reduced pressure, distilled water and dichloromethane were added to the residue and the organic layer was collected. The resulting organic layer was washed with saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:20 to 1:5), whereby the title compound (3.12 g, 84%) was obtained as colorless powder.

[0776]

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.38(4H,t,J=4.9Hz),

3.42(4H,t,J=4.8Hz), 3.51(2H,s), 7.25-7.29(1H,m), 7.30-7.33(4H,m).

MS (EI) m/z: 276M$^+$.

[0777]

[Referential Example 159]

1-Benzylpiperazine

To 1-benzyl-4-tert-butoxycarbonylpiperazine (3.12 g), saturated ethanol hydrochloride was added, followed by stirring for 90 minutes at room temperature. The solvent was distilled off under reduced pressure, followed by drying, whereby the title compound (2.73 g, 97%) was obtained as white powder.

[0778]

^{1}H-NMR (DMSO-d$_6$) δ: 3.05-3.67(9H,m), 4.38(2H,br), 7.35-7.70(5H,m), 9.61(1H,br).

MS (EI) m/z: 176M$^+$.

Elementary analysis for $C_{11}H_{16}N_2 \cdot 2HCl \cdot 0.2H_2O$

Calculated: C, 52.27; H, 7.34; Cl, 28.05; N, 11.27.

Found: C, 52.04; H, 7.36; Cl, 27.89; N, 11.24.

[0779]

[Referential Example 160]

1-Benzyl-4-sulfamoylpiperazine

Chlorosulfonyl isocyanate (0.35 ml) was dissolved in dichloromethane (5 ml). Under ice cooling, tert-butanol (0.21 ml) was added dropwise to the resulting solution, followed by stirring for 30 minutes. After the reaction mixture was added

dropwise to a solution of 1-benzylpiperazine dihydrochloride (0.25 g) in dichloromethane (20 ml) under ice cooling, triethylamine (0.28 ml) was added. The mixture was stirred for 30 minutes under ice cooling and then at room temperature for 1 hour. Distilled water and dichloromethane were added and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol : dichloromethane = 1:50 to 1:25), whereby 1-benzyl-[4-(N-tert-butoxycarbonyl)sulfamoyl]piperazine was obtained as colorless powder. To the resulting powder, saturated ethanol hydrochloride was added and the mixture was stirred at room temperature for 1 hour. After the solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium bicarbonate and dichloromethane were added to the residue and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (0.26 g, quant.) was obtained as colorless powder.

[0780]

^{1}H-NMR ($CDCl_3$) δ: 2.58(4H,t,J=4.9Hz), 3.22(4H,t,J=4.9Hz), 3.56(2H,s), 4.33(2H,br), 7.27-7.36(5H,m).

MS (EI) m/z: 255M^+.

[0781]

[Referential Example 161]

3,4-Bis(bromomethyl)-1-chlorobenzene

In acetonitrile (500 ml), 1-chloro-3,4-dimethylbenzene (20.0 ml) was dissolved and to the resulting solution, N-bromosuccinimide (53.0 g) and azoisobutyronitrile (1.20 g) were added, followed by heating under reflux for 1 hour. After cooling, the solvent was distilled off under reduced pressure and dichloromethane was then added to the residue. From the resulting mixture, the precipitate was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane), whereby the title compound (41.5 g, 93%) was obtained as a colorless oil.

[0782]

^{1}H-NMR ($CDCl_3$) δ: 4.59(2H,s), 4.61(2H,s), 7.27-7.36(3H,m).

MS (EI) m/z: 295M^+.

[0783]

[Referential Example 162]

1-Benzyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In ethanol (5 ml), 1-benzyl-4-sulfamoylpiperazine (251 mg) was dissolved. To the resulting solution, 3,4-bis(bromomethyl)-1-chlorobenzene (293 mg) and potassium carbonate (204 mg) were added, followed by heating under reflux for 3.5 hours. After cooling, the precipitate was filtered off. The filtrate was then distilled under reduced pressure and the residue was purified by chromatography on a silica gel column

(dichloromethane ~ ethanol : dichloromethane = 1:100), whereby the title compound (222 mg, 58%) was obtained.

[0784]

^{1}H-NMR ($CDCl_3$) δ: 2.37-2.58(4H,m), 3.24-3.41(4H,m), 3.53(2H,s), 4.64(4H,m), 7.13-7.34(8H,m).

MS (FAB) m/z: 392 [$(M+H)^+$, Cl^{35}], 394 [$(M+H)^+$, Cl^{37}].

[0785]

[Referential Example 163]

1-[(5-Chloroisoindol-2-yl)sulfonyl]piperazine

To a solution of 1-benzyl-4-[(5-chloroisoindol-2-yl)sulfonyl]piperazine (222 mg) in 1,2-dichloroethane (20 ml), 1-chloroethyl chloroformate (81 mg) was added under ice cooling. The resulting mixture was stirred for 15 minutes and then heated under reflux for 1 hour. After cooling, anhydrous methanol was added to the residue obtained by distilling off the solvent under reduced pressure. The mixture was heated under reflux for 11 hours. After cooling, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethanol : dichloromethane = 1:50 to 1:10), whereby the title compound (120 mg, 70%) was obtained.

[0786]

^{1}H-NMR ($CDCl_3$) δ: 2.96(4H,t,J=4.4Hz), 3.09-3.22(1H,br), 3.30(4H,t,J=4.4Hz), 4.65(4H,m), 7.14-7.35(3H,m).

MS (FAB) m/z: 302 [$(M+H)^+$, Cl^{35}], 304 [$(M+H)^+$, Cl^{37}].

[0787]

[Referential Example 164]

1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroisoindol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

[0788]

^{1}H-NMR ($CDCl_3$) δ: 3.35(2H,t,J=4.9Hz), 3.44(2H,t,J=4.9Hz), 3.49(2H,t,J=4.9Hz), 3.91(2H,t,J=4.9Hz), 4.65-4.68(4H,m), 7.17(1H,d,J=8.3Hz), 7.23(1H,s), 7.28(1H,m), 8.88(2H,s).

MS (EI) m/z: 486M^+.

[0789]

[Referential Example 165]

2-(Furan-2-yl)-5-(pyridin-4-yl)pyrazine

At room temperature, 2-chloro-5-(furan-2-yl)pyrazine (N. Sato, J. Heterocyclic Chem., 19, 407(1982)) (1.00 g) and (pyridin-4-yl)boronic acid (1.09 g) were suspended in a mixed solvent of dimethoxyethane (50 ml) and methanol (50 ml), followed by the successive addition of tetrakis(triphenylphosphine)palladium (O) (640 mg) and cesium fluoride (5.55 g). The resulting mixture was heated under reflux for 16 hours. After cooling, the reaction mixture was concentrated. Dichloromethane and water were added to the concentrate and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate, treated with activated carbon and filtered through Celite. After the

filtrate was concentrated to about 5 ml, petroleum ether (50 ml) was added to the concentrate. Yellow crystalline powder thus precipitated was collected by filtration and dried, whereby the title compound (716 mg, 58%) was obtained.

[0790]

^{1}H-NMR ($CDCl_3$) δ: 6.62(1H,dd,J=3.4,2.0Hz), 7.23(1H,d,J=3.4Hz), 7.65(1H,d,J=2.0Hz), 7.94(2H,d,J=6.4Hz), 8.77(2H,d,J=6.4Hz), 9.03(1H,d,J=1.5Hz), 9.07(1H,d,J=1.5Hz).

MS (FAB) m/z: 224 $(M+H)^+$.

[0791]

[Referential Example 166]

5-(Pyridin-4-yl)pyrazine-2-carboxylic acid

At room temperature, potassium permanganate (700 mg) and trioctylmethylammonium chloride (one drop) were dissolved in a mixed solvent of water (20 ml) and benzene (20 ml). To the resulting solution, 2-(furan-2-yl)-5-(pyridin-4-yl)pyrazine (700 mg) was added in portions, followed by stirring at room temperature for 17 hours. After ethanol was added to the reaction mixture to decompose excess potassium permanganate, the solvent was distilled off. To the residue, water (100 ml) was added and the mixture was filtered through Celite. To the filtrate, 1N hydrochloric acid was added to adjust its pH to 6. The solvent was distilled off until the precipitation of colorless crystals. The colorless crystals were collected by filtration, whereby the title compound (491 mg, 79%) was obtained.

[0792]

^1H-NMR (DMSO-d_6 with one drop of TEA) δ: 8.61(2H,d,J=5.9Hz), 9.04(2H,d,J=5.9Hz), 9.37(1H,s), 9.66(1H,s).

MS (FAB) m/z: 202 $(M+H)^+$.

Elementary analysis for $C_{10}H_7N_3O_2 \cdot 0.4H_2O$

Calculated: C, 57.64; H, 3.77; N, 20.16.

Found: C, 57.77; H, 3.79; N, 20.33.

[0793]

[Referential Example 167]

4-(3-Methylpyridin-4-yl)benzoic acid

In the same manner as in Referential Example 2, the title compound was obtained.

[0794]

^1H-NMR (DMSO-d_6) δ: 2.41(3H,s), 7.68(2H,d,J=8.3Hz), 7.93(1H,d,J=5.9Hz), 8.12(2H,d,J=8.3Hz), 8.85(1H,d,J=5.9Hz), 8.95(1H,s).

[0795]

[Referential Example 168] 4-Amidinobenzoic acid

In ethanol (250 ml), 4-cyanobenzoic acid (10 g) was suspended. Under ice cooling, a hydrochloric acid gas was introduced into the resulting suspension for 4 hours. After heating to room temperature, the reaction mixture was hermetically sealed and then allowed to stand for 18 hours. The reaction mixture was concentrated to dryness under reduced pressure. The residue was suspended in ethanol (250 ml) again,

followed by the introduction of an ammonia gas for 4 hours under ice cooling for saturation. After heating to room temperature, the reaction mixture was hermetically sealed and allowed to stand for 3 days. To the residue obtained by distilling off the solvent under reduced pressure, dilute hydrochloric acid was added to make the residue acidic, followed by concentration. The residue was purified by chromatography through a synthetic adsorbent ("Diaion (trade name) HP-20"; water ~ 20% acetonitrile - water). The crude purified product so obtained was dissolved in 20% methanol - dichloromethane and the resulting solution was purified by chromatography on a silica gel column (20% methanol - dichloromethane). To the resulting fraction, ethanolic hydrochloric acid was added and the mixture was concentrated. From the concentrate, colorless crystal powder was collected by filtration and dried, whereby ethyl 4-amidinobenzoate hydrochloride (5.25 g) was obtained as a crude purified product.

In 1N hydrochloric acid (100 ml), the resulting ethyl 4-amidinobenzoate hydrochloride (3.00 g) was dissolved at room temperature, followed by heating under reflux for 2 hours. The solvent was then distilled off under reduced pressure. Colorless crystalline powder so precipitated was collected by filtration and washed with a small amount of tetrahydrofuran, whereby the title compound (2.69 g, 94%) was obtained.

[0796]

^{1}H-NMR (DMSO-d_6) δ: 7.91(2H,d,J=8.3Hz), 8.12(2H,d,J=8.3Hz),

9.21(2H,br s), 9.49(2H,br s), 13.50(1H,br s).

MS (FAB) m/z: 165 $(M+H)^+$.

Elementary analysis for $C_8H_8N_2O_2 \cdot HCl \cdot H_2O$

Calculated: C, 43.95; H, 5.07; Cl, 16.22; N, 12.81.

Found: C, 44.08; H, 5.02; Cl, 16.00; N, 12.71.

[0797]

[Referential Example 169]

Ethyl 4-(4,5-dihydroimidazol-2-yl)benzoate

In ethanol (250 ml), 4-cyanobenzoic acid (5.00 g) was suspended. A hydrochloric acid gas was blown into the resulting suspension for 4 hours under ice cooling, followed by heating to room temperature. The reaction mixture was hermetically sealed and allowed to stand for 18 hours, followed by concentration to dryness under reduced pressure. To the residue, diethyl ether was added. Colorless crystals thus precipitated were collected by filtration and dried, whereby ethyl 4-[1-ethoxy)iminomethyl]benzoate hydrochloride (5.80 g, 66%) was obtained.

The resulting ethyl 4-[1-ethoxy)iminomethyl]benzoate hydrochloride (2.00 g) was dissolved in ethanol (30 ml). Under ice cooling, ethylenediamine (0.52 ml) was added to the resulting solution, followed by heating to room temperature. The reaction mixture was stirred overnight. To the residue obtained by distilling off the solvent under reduced pressure, dilute hydrochloric acid was added to make it acidic, followed by concentration again. The residue was purified by

chromatography through a synthetic adsorbent ("Diaion (trade name) HP-20"; water ~ 50% acetonitrile-water). Ethanolic hydrochloric acid was added to the resulting fraction and the mixture was concentrated. Colorless crystalline powder precipitated by the addition of tetrahydrofuran was collected by filtration and dried, whereby the title compound (1.63 g, 19%) was obtained.

[0798]

^{1}H-NMR (DMSO-d_6) δ: 1.35(3H,t,J=7.3Hz), 4.02(4H,s), 4.37(2H,q,J=7.3Hz), 8.17(2H,d,J=8.8Hz), 8.21(2H,d,J=8.8Hz), 11.08(2H,br s).

MS (FAB) m/z: 219 $(M+H)^+$.

Elementary analysis for $C_{12}H_{14}N_2O_2 \cdot HCl \cdot 0.2H_2O$

Calculated: C, 55.80; H, 6.01; Cl, 13.72; N, 10.84.

Found: C, 55.81; H, 5.99; Cl, 13.93; N, 11.00.

[0799]

[Referential Example 170]

5-(4,5-Dihydroimidazol-2-yl)benzoic acid

In the same manner as in Referential Example 8, the title compound was obtained using ethyl 4-(4,5-dihydroimidazol-2-yl)benzoate as a raw material.

[0800]

^{1}H-NMR (DMSO-d_6) δ: 4.03(4H,s), 8.15(4H,s), 10.99(2H,br s).

MS (FAB) m/z: 191 $(M+H)^+$.

Elementary analysis for $C_{10}H_{10}N_2O_2 \cdot HCl \cdot 1.2H_2O$

Calculated: C, 48.38; H, 5.44; Cl, 14.28; N, 11.28.

Found: C, 48.37; H, 5.29; Cl, 14.64; N, 11.12.

[0801]

[Referential Example 171]

4-(4-Metylphenyl)pyridine

In the same manner as in Referential Example 2, a reaction was effected, whereby the title compound was obtained.

[0802]

^{1}H-NMR ($CDCl_3$) δ: 2.42(3H,s), 7.30(2H,d,J=8.3Hz), 7.51(2H,d,J=5.9Hz), 7.55(2H,d,J=8.3Hz), 8.64(2H,d,J=5.9Hz).

[0803]

[Referential Example 172]

2-Amino-4-(4-methylphenyl)pyridine

Under an argon gas, 4-(4-methylphenyl)pyridine (2.74 g) was dissolved in N,N-dimethylaniline (10 ml), followed by the addition of sodium amide (1.40 g) at room temperature. After the resulting mixture was stirred at 110°C for 2 days, the reaction mixture was cooled to room temperature. Brown powder precipitated by the addition of water was collected by filtration. The powder was further purified by chromatography on a silica gel column (ethyl acetate : toluene = 1:1). After concentration of the resulting fraction, hexane was added and powder thus precipitated was collected by filtration and dried, whereby the title compound (1.40 g, 47%) was obtained.

[0804]

^{1}H-NMR ($CDCl_3$) δ: 2.40(3H,s), 4.45(2H,br s), 6.69(1H,d,J=1.5Hz),

6.88(1H,dd,J=5.4,1.5Hz), 7.26(2H,d,J=8.3Hz), 7.49(2H,d,J=8.3Hz), 8.11(1H,d,J=5.4Hz)

MS (FAB) m/z: 185 $(M+H)^+$.

[0805]

[Referential Example 173]

2-Diacetylamino-4-(4-methylphenyl)pyridine

2-Amino-4-(4-methylphenyl)pyridine (1.27 g) was dissolved in dichloromethane (50 ml). Under ice cooling, N,N-diisopropylethylamine (1.80 ml) and acetyl chloride (735 µl) were successively added dropwise to the resulting solution. After heating to room temperature, the reaction mixture was added again with N,N-diisopropylethylamine (0.90 ml) and acetyl chloride (800 µl). The mixture was stirred for 18 hours. Methanol was added to the reaction mixture. Dilute hydrochloric acid and ethyl acetate were then added to the residue obtained by distilling off the solvent and the organic layer was collected. After the resulting organic layer was dried over anhydrous magnesium sulfate, the filtrate was concentrated. The residue was dissolved in methanol. Crystals precipitated by the addition of water were collected by filtration and dried, whereby the title compound (1.39 g, 75%) was obtained.

[0806]

^{1}H-NMR ($CDCl_3$) δ: 2.33(6H,s), 2.42(3H,s), 7.31(2H,d,J=8.3Hz), 7.43(1H,d,J=1.5Hz), 7.53-7.59(3H,m), 8.61(1H,d,J=4.9Hz).

MS (FAB) m/z: 269 $(M+H)^+$.

Elementary analysis for $C_{16}H_{16}N_2O_2$

Calculated: C, 71.62; H, 6.01; N, 10.44.

Found: C, 71.28; H, 5.98; N, 10.19.

[0807]

[Referential Example 174]

4-(2-Acetylaminopyridin-4-yl)benzoic acid

In water (4 ml), anhydrous magnesium sulfate (161 mg) was dissolved. To the resulting solution, 2-diacetylamino-4-(4-methylphenyl)pyridine (108 mg) was suspended. Potassium permanganate (223 mg) was added to the resulting suspension, followed by heating under reflux for 2 hours. After removal of manganese dioxide by filtration, dilute hydrochloric acid and dichloromethane were added to the filtrate and the water layer was obtained by separation. The water layer was concentrated to about 20 ml and the crystals thus precipitated were collected by filtration and dried, whereby the title compound (64 mg, 62%) was obtained.

[0808]

^{1}H-NMR (DMSO-d_6) δ: 2.19(3H,s), 7.58(1H,d,J=5.9Hz), 7.87(2H,d,J=8.3Hz), 8.04(1H,s), 8.11(2H,d,J=8.3Hz), 8.33(1H,s), 8.43(1H,d,J=5.9Hz), 11.23(1H,br s).

MS (FAB) m/z: 257 $(M+H)^+$.

[0809]

[Referential Example 175]

Methyl 4-(2-aminopyridin-4-yl)benzoate

In the same manner as in Referential Example 9, a reaction was effected using 4-(2-acetylaminopyridin-4-yl)benzoic acid as a raw material, whereby the title compound was obtained.

[0810]

^{1}H-NMR ($CDCl_3$) δ: 3.95(3H,s), 4.53(2H,br s), 6.72(1H,d,J=1.5Hz), 6.90(1H,dd,J=5.4,1.5Hz), 7.65(2H,d,J=8.3Hz), 8.12(2H,d,J=8.3Hz), 8.16(1H,d,J=5.4Hz).

MS (FAB) m/z: 229 $(M+H)^+$.

Elementary analysis for $C_{13}H_{12}N_2O_2$

Calculated: C, 68.41; H, 5.30; N, 12.27.

Found: C, 68.30; H, 5.27; N, 12.36.

[0811]

[Referential Example 176]

Methyl 4-[2-(N-tert-butoxycarbonylamino)pyridin-4-yl)benzoate

In the same manner as in Referential Example 10, the title compound was obtained.

[0812]

^{1}H-NMR (DMSO-d_6) δ: 1.50(9H,s), 3.89(3H,s), 7.38(1H,dd,J=5.4,1.5Hz), 7.86(2H,d,J=8.3Hz), 8.10(2H,d,J=8.3Hz), 8.14(1H,d,J=1.5Hz), 8.35(1H,d,J=5.4Hz), 9.89(1H,br s).

[0813]

[Referential Example 177]

4-[2-(N-tert-butoxycarbonylamino)pyridin-4-yl)benzoic acid

In the same manner as in Referential Example 11, the title compound was obtained.

[0814]

^{1}H-NMR (DMSO-d_6) δ: 1.49(9H,s), 7.38(1H,dd,J=5.4,1.0Hz), 7.83(2H,d,J=8.3Hz), 8.07(2H,d,J=8.3Hz), 8.12(1H,d,J=1.0Hz), 8.33(1H,d,J=5.4Hz), 9.93(1H,br s), 13.07(1H,br s).

[0815]

[Referential Example 178]

1-[4-(2-Azidomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine (300 mg) was dissolved. To the resulting solution, triphenylphosphine (301 mg) and carbon tetrabromide (572 mg) were added, followed by stirring at room temperature for 5 minutes. An aqueous solution of sodium bicarbonate and dichloromethane were added and the organic layer was collected. After the resulting organic layer was dried over anhydrous sodium sulfate, N,N-dimethylformamide (10 ml) was added and only dichloromethane was distilled off. To the N,N-dimethylformamide solution containing the bromo-compound, sodium azide (215 mg) was added, followed by stirring at an external temperature of about 100°C for 90 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent. Dichloromethane and water were added to the

residue and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby the title compound (159 mg, 51%) was obtained.

[0816]

^{1}H-NMR ($CDCl_3$) δ: 3.16(4H,br), 3.30-4.10(4H,br), 4.57(2H,s), 7.40-7.45(3H,m), 7.52(1H,s), 7.60(1H,dd,J=8.8 and 2.0Hz), 7.64(2H,d,J=8.3Hz), 7.76(1H,dd,J=8.3 and 1.5Hz), 7.90-7.96(3H,m), 8.31(1H,d,J=1.5Hz), 8.65(1H,d,J=5.4Hz).

MS (FAB) m/z: 547 [$(M+H)^+$, Cl^{35}], 549 [$(M+H)^+$, Cl^{37}].

[0817]

[Referential Example 179]

Methyl 4-(2-methylpyridin-4-yl)benzoate hydrochloride

In methanol (100 ml), 4-(2-methylpyridin-4-yl)benzoic acid hydrochloride (5.00 g) was dissolved. To the resulting solution, thionyl chloride (1.73 ml) was added dropwise, followed by heating under reflux for 3.5 hours. The reaction mixture was distilled to remove the solvent and pale brown crystals thus precipitated were washed with ethyl acetate, whereby the title compound (4.70 g, 89%) was obtained.

[0818]

[Referential Example 180]

Methyl 4-(2-bromomethylpyridin-4-yl)benzoate

In a mixed solution of carbon tetrachloride and an aqueous solution of sodium bicarbonate, methyl 4-(2-methylpyridin-4-yl)benzoate hydrochloride (100 mg) was dissolved. The organic layer collected by separation was dried over anhydrous sodium sulfate. After the insoluble matter was filtered off, N-bromosuccinic imide (68 mg) and 2,2′-azoisobutylonitrile (6 mg) were added to the filtrate, followed by heating under reflux for 1 hour. The reaction mixture was diluted with dichloromethane, washed with water and then dried over anhydrous sodium sulfate. The residue obtained by concentration under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (41 mg, 35%) was obtained.

[0819]

^{1}H-NMR ($CDCl_3$) δ: 3.96(3H,s), 4.63(2H,s), 7.46(1H,dd,J=4.9,1.5Hz), 7.68(1H,d,J=1.5Hz), 7.71(2H,d,J=8.3Hz), 8.16(2H,d,J=8.3Hz), 8.69(1H,d,J=4.9Hz).

Elementary analysis for $C_{14}H_{12}BrNO_2$

Calculated: C, 54.92; H, 3.95; Br, 26.10; N, 4.58.

Found: C, 54.95; H, 3.96; Br, 25.85; N, 4.33.

[0820]

[Referential Example 181]

Methyl 4-(2-cyanomethylpyridin-4-yl)benzoate

In the same manner as in Referential Example 56, the title compound was obtained.

[0821]

^{1}H-NMR ($CDCl_3$) δ: 3.97(3H,s), 4.03(2H,s), 7.51(1H,d,J=5.4Hz), 7.67(1H,s), 7.71(2H,d,J=8.3Hz), 8.17(2H,d,J=8.3Hz), 8.67(1H,d,J=5.4Hz).

Elementary analysis for $C_{15}H_{12}N_2O_2$

Calculated: C, 71.42; H, 4.79; N, 11.10.

Found: C, 71.13; H, 4.82; N, 11.05.

[0822]

[Referential Example 182]

Methyl 4-[2-(2-aminoethyl)pyridin-4-yl]benzoate dihydrochloride

In methanol (5 ml), methyl 4-(2-cyanomethylpyridin-4-yl)benzoate (190 mg) was dissolved. The resulting solution was subjected to catalytic reduction by the addition of 10% palladium-carbon (190 mg) and concentrated hydrochloric acid (5 drops) at room temperature under normal pressure for 24 hours. After the removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. Ethyl acetate was added to the concentrate. Pale yellow crystals thus precipitate were collected by filtration and then dried, whereby the title compound (141 mg, 57%) was obtained.

[0823]

^{1}H-NMR (DMSO-d_6) δ: 3.21-3.39(4H,m), 3.90(3H,s), 7.90-8.18(8H,m), 8.76(1H,d,J=5.4Hz).

MS (FAB) m/z: 257 $(M+H)^+$.

[0824]

[Referential Example 183]

Methyl 4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoate

In the same manner as in Referential Example 10, the title compound was obtained.

[0825]

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 3.07(2H,t,J=6.4Hz), 3.60(2H,q,J=6.4Hz), 3.96(3H,s), 5.14(1H,br s), 7.39(1H,dd,J=5.4 and 1.5Hz), 7.41(1H,br s), 7.70(2H,d,J=8.3Hz), 8.15(2H,d,J=8.3Hz), 8.62(1H,d,J=5.4Hz).

MS (FAB) m/z: 357 $(M+H)^+$.

[0826]

[Referential Example 184]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

At room temperature, 2-methoxycarbonylpyrazine (1.00 g) was dissolved in methanol. The resulting solution was subjected to catalytic reduction by the addition of 10% palladium-carbon (100 mg) for 2 hours under normal pressure. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (5% methanol-dichloromethane), whereby 6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (880 mg, 86%) was obtained as a yellow oil.

The resulting 6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (440 mg) was dissolved in dichloromethane (5 ml), followed by the addition of N,N-diisopropylethylamine (594 μl) and 6-(chloronaphthalen-2-yl)sulfonyl chloride (810 mg). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. The filtrate was then concentrated. The residue thus obtained was purified by chromatography on a silica gel column (2% methanol - dichloromethane), whereby the title compound (279 mg, 25%) was obtained as a pale yellow oil.

[0827]

^{1}H-NMR ($CDCl_3$) δ: 3.32(4H,s), 3.71(3H,s), 4.68(1H,br s), 7.43(1H,d,J=6.8Hz), 7.55(1H,dd,J=8.8,2.0Hz), 7.86-7.94(3H,m), 8.19(1H,dd,J=8.8,2.0Hz), 8.54(1H,br s).

MS (FAB) m/z: 367 [$(M+H)^+$, Cl^{35}], 369 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{16}H_{15}ClN_2O_4S$

Calculated: C, 52.39; H, 4.12; N, 7.64.

Found: C, 52.31; H, 4.21; N, 7.55.

[0828]

[Referential Example 185]

1-(4-Bromobenzoyl)-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

In the same manner as in Referential Example 184, 6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine was obtained, followed by reaction with 4-bromobenzoyl chloride, whereby the

title compound was obtained.

[0829]

^{1}H-NMR ($CDCl_3$) δ: 3.20-3.70(7H,m), 4.71(1H,br s), 7.16(1H,d,J=6.4Hz), 7.48(4H,s).

MS (FAB) m/z: 325 [$(M+H)^+$, Br^{79}], 327 [$(M+H)^+$, Br^{81}].

[0830]

[Referential Example 186]

4-(4-Bromobenzoyl)-1-[(6-chloronaphthalen-2-yl)sulfonyl-5-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

In the same manner as in Referential Example 165, the title compound was obtained.

[0831]

^{1}H-NMR ($CDCl_3$) δ: 3.40-3.90(7H,m), 7.33(2H,d,J=8.3Hz), 7.48(2H,d,J=8.3Hz), 7.60-7.66(2H,m), 7.79(1H,dd,J=8.8,2.0Hz), 7.92-7.99(3H,m), 8.43(1H,br s).

MS (FAB) m/z: 549 [$(M+H)^+$, Br^{79}], 551 [$(M+H)^+$, Br^{81}].

Elementary analysis for $C_{23}H_{18}BrClN_2O_5S$

Calculated: C, 50.24; H, 3.30; N, 5.10; S, 5.83.

Found: C, 50.34; H, 3.37; N, 5.05; S, 5.81.

[0832]

[Referential Example 187]

4-[3-(Aminomethyl)phenyl]benzoic acid hydrochloride

In the same manner as in Referential Example 2, the title compound was obtained.

[0833]

^{1}H-NMR (DMSO-d_6) δ: 4.11(2H,s), 7.49-7.58(2H,m), 7.76(1H,d,J=6.8Hz), 7.83(2H,d,J=8.8Hz), 7.92(1H,br s), 8.05(2H,d,J=8.3Hz).

[0834]

[Referential Example 188]

4-[3-[(tert-Butoxycarbonylamino)methyl]phenyl]benzoic acid

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 4.41(2H,d,J=5.4Hz), 4.94(1H,br s), 7.28-7.37(1H,m), 7.44(1H,t,J=7.3Hz), 7.50-7.60(2H,m), 7.68(2H,d,J=8.3Hz), 8.10-8.23(2H,m).

[0835]

[Referential Example 189]

Ethyl 2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate

In ethanol (20 ml), 4-pyridinecarboxyamidrazone (1.48 g) was dissolved. To the resulting solution, diethyl ketomalonate (1.65 ml) was added dropwise at room temperature, followed by stirring for 13 hours. After heating under reflux for 4 hours, the reaction mixture was cooled. Yellow crystals thus precipitated were collected by filtration and dried, whereby the title compound (1.50 g, 56%) was obtained.

[0836]

^{1}H-NMR (DMSO-d_6) δ: 1.31(3H,t,J=7.3Hz), 4.36(2H,q,J=7.3Hz), 7.98(2H,d,J=6.3Hz), 8.86(2H,d,J=6.3Hz).

MS (FAB) m/z: 247 $(M+H)^+$.

Elementary analysis for $C_{11}H_{10}N_4O_3 \cdot 0.2H_2O$

Calculated: C, 52.88; H, 4.20; N, 22.43.

Found: C, 52.78; H, 4.36; N, 22.66.

[0837]

[Referential Example 190]

2,5-Dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylic acid

In the same manner as in Referential Example 11, the title compound was obtained.

[0838]

^{1}H-NMR (DMSO-d_6 (containing a small amount of trifluoroacetic acid)) δ: 8.31(2H,d,J=6.4Hz), 8.86(2H,d,J=6.4Hz).

MS (FAB) m/z: 218 $(M+H)^+$.

Elementary analysis for $C_9H_6N_4O_3 \cdot 0.2H_2O$

Calculated: C, 48.74; H, 2.91; N, 25.26.

Found: C, 48.58; H, 2.87; N, 25.21.

[0839]

[Referential Example 191]

2,6-Bis(methoxycarbonylmethyl)-1,4-dibenzylpiperazine

In a shield tube, bis(3-methoxycarbonyl-2-propylenyl)benzylamine (104 mg) and benzylamine (60.0 µl) were dissolved in methanol (5 ml). After the tube was hermetically sealed, the resulting solution was stirred under heat at an external temperature of about 100 to 110°C for 63 hours. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (n-hexane : ethyl acetate = 3:1), whereby the title compound

(123 mg, 88%) was obtained as a yellow oil.

[0840]

^{1}H-NMR ($CDCl_3$) δ: 2.25-2.60(8H,each m), 3.15-3.85(12H,m), 7.15-7.30(10H,m).

MS (FAB) m/z: 411 $(M+H)^+$.

[0841]

[Referential Example 192]

cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In methanol (70 ml) and hydrochloric acid (570 µl), 2,6-bis(methoxycarbonylmethyl)-1,4-dibenzylpiperazine (1.33 g) was dissolved. To the resulting solution, palladium hydroxide (149 mg) was added, followed by catalytic reduction at room temperature for 4 hours. After the removal of the catalyst by filtration, the residue was distilled under reduced pressure to remove the solvent. Dichloromethane (70 ml) and N,N-diisopropylethylamine (2.70 ml) were added to the resulting residue to dissolve the latter in the former, followed by the addition of (6-chloronaphthalen-2-yl)sulfonyl chloride (495 mg). The mixture was stirred for 3 hours under stirring. To the reaction mixture, (6-chloronaphthalen-2-yl)sulfonyl chloride (200 mg) and N,N-diisopropylethylamine (180 µl) were added. The resulting mixture was stirred for 12.5 hours, while gradually heated to room temperature from an external

temperature of about 0°C. Since the reaction was not completed, (6-chloronaphthalen-2-yl)sulfonyl chloride (101 mg) and N,N-diisopropylethylamine (90 μl) were added further and the mixture was stirred for 4.5 hours while heated gradually to room temperature from an external temperature of about 0°C. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (5% methanol - dichloromethane, n-hexane : ethyl acetate = 1:2), whereby cis-form (226 mg, 15%) and trans-form (1.07 g, 73%) of the title compounds, were obtained respectively, as pale yellow amorphous powder.

[0842]

cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 2.00-2.10(2H,m), 2.20-2.30(2H,m), 2.35-2.45(2H,m), 2.85(1H,br), 3.20-3.30(2H,m), 3.69(6H,s), 3.70-3.80(2H,m), 7.50-7.60(1H,m), 7.70-7.80(1H,m), 7.85-7.95(3H,m), 8.30(1H,s).

[0843]

trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

^{1}H-NMR ($CDCl_3$) δ: 2.40-2.60(5H,m), 2.80-2.90(2H,m), 3.10-3.20(2H,m), 3.45-3.55(2H,m), 3.69(6H,s), 7.50-7.60(1H,m), 7.70-7.80(1H,m), 7.85-7.95(3H,m), 8.29(1H,s).

MS (FAB) m/z: 455 [$(M+H)^+$, Cl^{35}], 457 [$(M+H)^+$, Cl^{37}].

[0844]

[Referential Example 193]

trans-2,6-Bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (8 ml), the trans-2,6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (79.7 mg) was dissolved. Under ice cooling, N,N-diisopropylethylamine (68.0 μl) and a solution of 4-bromobenzoyl chloride(51.0 mg) in dichloromethane (dichloromethane: 2 ml) were added to the resulting solution, followed by stirring at room temperature for 5.5 hours. Water was added to the reaction mixture and the organic layer was collected. The resulting organic layer was washed with saturate saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (n-hexane : ethyl acetate = 1:1), whereby the title compound (113 mg, 98%) was obtained as pale yellow amorphous powder.

[0845]

^{1}H-NMR ($CDCl_3$) δ: 2.80-2.90(4H,m), 3.20-3.40(4H,m), 3.63(6H,s), 4.20-4.30(2H,m), 7.23(2H,d,J=8.3Hz), 7.50(2H,d,J=8.3Hz), 7.55-7.65(1H,m), 7.70-7.80(1H,m), 7.90-7.95(3H,m), 8.30(1H,s).

MS (FAB) m/z: 637 [$(M+H)^+$, Br^{79}, Cl^{35}], 639 [$(M+H)^+$, Br^{79}, Cl^{37} and Br^{81}, Cl^{35}], 641 [$(M+H)^+$, Br^{81}, Cl^{37}].

[0846]

[Referential Example 194]

cis-2,6-Bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 193, the title compound was obtained.

[0847]

^{1}H-NMR ($CDCl_3$) δ: 2.40-2.75(4H,m), 2.80-3.20(2H,m), 3.55-4.00(2H,m), 3.68(6H,s), 4.20-4.40(1H,m), 5.00-5.20(1H,m), 7.10-7.15(2H,m), 7.45-7.55(2H,m), 7.55-7.65(1H,m), 7.70-7.80(1H,m), 7.90-7.95(3H,m), 8.30(1H,s).

MS (FAB) m/z: 637 [$(M+H)^+$, Br^{79}, Cl^{35}], 639 [$(M+H)^+$, Br^{79}, Cl^{37} and Br^{81}, Cl^{35}], 641 [$(M+H)^+$, Br^{81}, Cl^{37}].

[0848]

[Referential Example 195]

trans-2,6-Bis(carbamoylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 35, the title compound was obtained using trans-2,6-bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0849]

^{1}H-NMR ($CDCl_3$) δ: 2.5-2.65(2H,m), 3.10-3.30(4H,m), 3.40-3.50(2H,m), 4.20-4.30(2H,m), 6.34(2H,broads), 6.59(2H,br s), 7.14(2H,d,J=8.3Hz), 7.31(2H,d,J=8.3Hz), 7.50-7.60(1H,m),

7.65-7.75(1H,m), 7.85-7.95(3H,m), 8.26(1H,s).

[0850]

[Example 1]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

At room temperature, 1-[4-(4-pyridyl)benzoyl]piperazine ditrifluoroacetate (1.19 g) was suspended in dichloromethane (100 ml), followed by the addition of diisopropylethylamine (1.68 ml) and 6-chloro-2-naphthylsulfonyl chloride (WO/96/10022) (691 mg). After stirring at room temperature for 2 hours, the reaction mixture was purified by chromatography on a silica gel column (2% methanol - dichloromethane). To the resulting fraction, ethanolic 1N hydrochloric acid was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with tetrahydrofuran, whereby the title compound (1.05 g, 81%) was obtained as a colorless solid.

[0851]

^{1}H-NMR (DMSO-d_6) δ: 2.95-3.25(4H,m), 3.43(2H,br s), 3.60(2H,br s), 7.56(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.5Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.01(2H,d,J=8.3Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.40(4H,m), 8.51(1H,s), 8.94(2H,d,J=6.8Hz).

MS (FAB) m/z: 492 [(M+H)$^+$, Cl^{35}], 494 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}N_3O_3ClS \cdot HCl \cdot 0.5H_2O$

Calculated: C, 58.10; H, 4.50; N, 7.82; Cl, 13.19; S, 5.97.

Found: C, 58.12; H, 4.67; N, 7.66; Cl, 13.12; S, 6.10.

[0852]

[Example 2]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In dichloromethane (30 ml), 4-tert-butoxycarbonyl-2-ethoxycarbonyl-1-[4-(4-pyridyl)benzoyl]piperazine (514 mg) was dissolved, followed by the addition of trifluoroacetic acid (30 ml) under ice cooling. After stirring at room temperature for 45 minutes, the residue obtained by distilling off the solvent was suspended in dichloromethane (100 ml) under ice cooling, followed by the addition of diisopropylethylamine (1.02 ml) and 6-chloro-2-naphthylsulfonyl chloride (WO96/10022) (366 mg). After stirring at room temperature for one hour, the reaction mixture was purified as was by chromatography on a silica gel column (1% methanol - dichloromethane). To the resulting fraction, ethanolic 1N hydrochloric acid was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with ethanol, whereby the title compound (308 mg, 43%) was obtained as a colorless solid.

[0853]

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.30(3H,m), 2.60-5.40(9H,m), 7.50(2/3H,d,J=8.3Hz), 7.57(4/3H,d,J=7.8Hz), 7.74(1H,dd,J=9.0,1.7Hz), 7.83(1H,d,J=8.8Hz),

8.00(2/3H,d,J=7.8Hz), 8.04(4/3H,d,J=8.3Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.35(4H,m), 8.55(1H,s), 8.92(2H,d,J=4.9Hz).

MS (FAB) m/z: 564 [(M+H)$^+$, Cl^{35}], 566 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}N_3O_5ClS \cdot HCl \cdot 0.5H_2O$

Calculated: C, 57.15; H, 4.63; N, 6.89; Cl, 11.63; S, 5.26.

Found: C, 56.95; H, 4.68; N, 6.70; Cl, 11.36; S, 5.30.

[0854]

[Example 3]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid hydrochloride

In a mixed solvent of ethanol (1 ml), tetrahydrofuran (1 ml) and water (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride (152 mg) obtained in Example 2 was dissolved under ice cooling, followed by the dropwise addition of a 1N aqueous solution of sodium hydroxide. The reaction mixture was stirred at room temperature for 90 minutes. After concentration under reduced pressure, 1N hydrochloric acid was added to the reaction mixture to make it weakly acidic. The colorless solid so precipitated was collected by filtration, followed by drying, whereby the title compound (62 mg, 42%) was obtained as a colorless solid.

[0855]

^{1}H-NMR (DMSO-d_6) δ: 2.65-5.30(7H,m), 7.49(4/5H,d,J=7.7Hz), 7.56(6/5H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.0Hz),

7.82(1H,d,J=8.3Hz), 7.95-8.05(2H,m), 8.19(1H,d,J=8.3Hz), 8.20-8.35(4H,m), 8.53(1H,s), 8.92(2H,d,J=5.4Hz).

MS (FAB) m/z: 536 [$(M+H)^+$, Cl^{35}], 538 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{22}N_3O_5ClS \cdot 0.9HCl \cdot 1.2H_2O$

Calculated: C, 54.92; H, 4.32; N, 7.12; Cl, 11.41; S, 5.43.

Found: C, 54.94; H, 4.42; N, 6.83; Cl, 11.31; S, 5.33.

[0856]

[Example 4]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)nicotinyl]piperazine hydrochloride

In dichloromethane (10 ml), 6-(4-pyridyl)nicotinic acid hydrochloride (96 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (150 mg) were suspended, followed by the addition of 1-hydroxybenzotriazole (48 mg) and N-methylmorpholine (155 µl). After the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (102 mg) under ice cooling, the resulting mixture was stirred at room temperature for 16 hours. Owing to the slow reaction, N,N-dimethylformamide (10 ml) was added to the reaction mixture and the resulting mixture was stirred for 3 days. After completion of the reaction, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (1% methanol - dichloromethane). The solvent was then distilled off. To the residue, tetrahydrofuran and ethanolic 1N hydrochloric acid were added and the solid so precipitated was collected by filtration and

dried, whereby the title compound (105 mg, 55%) was obtained as a colorless solid.

[0857]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.25(4H,m), 3.46(2H,br s), 3.76(2H,br s), 7.74(1H,dd,J=8.5,1.7Hz), 7.83(1H,d,J=8.8Hz), 8.07(1H,dd,J=7.8,1.5Hz), 8.19(1H,d,J=8.8Hz), 8.28(1H,s), 8.29(1H,d,J=8.8Hz), 8.42(1H,d,J=8.3Hz), 8.51(1H,s), 8.65(2H,d,J=6.4Hz), 8.80(1H,m), 9.01(2H,d,J=5.9Hz).

MS (FAB) m/z: 493 [$(M+H)^+$, Cl^{35}], 495 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{21}N_4O_3ClS \cdot HCl \cdot H_2O$

Calculated: C, 54.85; H, 4.42; N, 10.23; Cl, 12.95; S, 5.86.

Found: C, 54.57; H, 4.51; N, 10.06; Cl, 13.08; S, 5.87.

[0858]

[Example 5]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-(3-pyridyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate as raw materials, whereby the title compound was obtained as a colorless solid.

[0859]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.25(4H,m), 3.47(2H,br s), 3.73(2H,br s), 7.51(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.8-7.9(3H,m), 7.92(1H,dd,J=7.8,5.4Hz), 8.19(1H,d,J=8.8Hz),

8.25-8.30(2H,m), 8.50(1H,s), 8.55-8.65(1H,m), 8.75-8.85(1H,m), 9.14(1H,d,J=2.0Hz).

MS (FAB) m/z: 492 [$(M+H)^+$, Cl^{35}], 494 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}N_3O_3ClS \cdot 0.85HCl \cdot H_2O$

Calculated: C, 57.72; H, 4.63; N, 7.77; Cl, 12.12; S, 5.93.

Found: C, 57.44; H, 4.62; N, 7.68; Cl, 11.99; S, 5.83.

[0860]

[Example 6]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (300 mg) obtained in Example 1 was dissolved, followed by the addition of 3-chloroperbenzoic acid (382 g) at -20°C. The resulting mixture was stirred at -20°C for 21 hours. An aqueous solution of sodium sulfite was added to decompose an excess peroxide. Dichloromethane and a saturated aqueous solution of sodium bicarbonate were added and the organic layer was collected. After drying the organic layer over anhydrous magnesium sulfate, the residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (2-5% methanol - dichloromethane). After the solvent was distilled off, ether was added to the residue to solidify it, followed by collection through filtration, whereby the title compound (200 mg, 63%) was obtained as a colorless solid.

[0861]

^{1}H-NMR ($CDCl_3$) δ: 2.90-3.40(4H,m), 3.40-4.20(4H,m), 7.43(2H,d,J=8.3Hz), 7.47(2H,d,J=7.3Hz), 7.55-7.65(3H,m), 7.76(1H,dd,J=8.8,1.5Hz), 7.90-8.00(3H,m), 8.26(2H,d,J=7.3Hz), 8.31(1H,s).

MS (FAB) m/z: 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}N_3O_4ClS \cdot 0.8H_2O$

Calculated: C, 59.78; H, 4.55; N, 8.04; Cl, 6.79; S, 6.14.

Found: C, 59.82; H, 4.45; N, 7.94; Cl, 6.85; S, 6.29.

[0862]

[Example 7]

1-[4-(2-Aminopyridin-5-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In a mixed solvent of dichloromethane (1 ml) and ethanol (1 ml), 1-[4-[2-tert-butoxycarbonylamino)pyridin-5-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (128 mg) was dissolved, followed by the addition of a saturated ethanol hydrochloride solution (10 ml) under ice cooling. After stirring at room temperature for 1 minute, the solvent was distilled off. Isopropanol was added to the residue for crystallization. The crystals so obtained were collected by filtration and dried, whereby the title compound (88 mg, 68%) was obtained as a colorless solid.

[0863]

^{1}H-NMR ($DMSO-d_6$) δ: 3.00-3.20(4H,m), 3.30-3.90(4H,m),

7.05(1/2H,d,J=8.8Hz), 7.06(1/2H,d,J=8.8Hz), 7.43(2H,d,J=8.3Hz), 7.67(2H,d,J=8.3Hz), 7.73(1H,d,J=8.3Hz), 7.82(1H,d,J=8.8Hz), 7.90-8.10(2H,br), 8.18(1H,d,J=8.3Hz), 8.25-8.35(4H,m), 8.50(1H,s).

MS (FAB) m/z: 507 [$(M+H)^+$, Cl^{35}], 509 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{23}ClN_4O_3S\cdot HCl\cdot 1.2H_2O\cdot 0.8iPrOH$

Calculated: C, 55.56; H, 5.52; N, 9.13; Cl, 11.55; S, 5.22.

Found: C, 55.40; H, 5.24; N, 8.85; Cl, 11.79; S, 5.50.

[0864]

[Example 8]

1-[4-(4-Aminophenyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was conducted using 1-[4-[4-(tert-butoxycarbonylamino)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained as a colorless solid.

[0865]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.20(4H,m), 3.25-3.80(4H,m), 6.68(2H,d,J=8.3Hz), 7.32(2H,d,J=8.3Hz), 7.39(2H,d,J=8.3Hz), 7.54(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 8.18(1H,dd,J=8.8Hz), 8,25-8.40(2H,m), 8.50(1H,br s).

MS (FAB) m/z: 506 [$(M+H)^+$, Cl^{35}], 508 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_3S\cdot 0.2HCl$

Calculated: C, 63.18; H, 4.75; N, 8.19; Cl, 8.29; S, 6.25.

Found: C, 62.93; H, 4.93; N, 7.91; Cl, 7.99; S, 6.36.

[0866]

[Example 9]

1-[4-(2-Aminothiazol-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was effected using 4-(2-aminothiazol-4-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0867]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.20(4H,m), 3.30-3.90(4H,m), 7.26(1H,s), 7.41(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.79(2H,d,J=8.3Hz), 7.82(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,br s).

MS (FAB) m/z: 513 [$(M+H)^+$, Cl^{35}], 515 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}N_4O_3ClS_2 \cdot HCl \cdot 0.3H_2O$

Calculated: C, 51.95; H, 4.11; N, 10.10; Cl, 12.78; S, 11.56.

Found: C, 51.99; H, 4.19; N, 10.03; Cl, 12.61; S, 11.45.

[0868]

[Example 10]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[imidazol-4(5)-yl]benzoyl]piperazine hydrochloride

In dichloromethane (5 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-[1-triphenylmethylimidazol-4(5)-yl]benzoyl]piperazine (303 mg) was dissolved, followed by the

addition of a saturated ethanol hydrochloride solution (30 ml) under ice cooling. After stirring at room temperature for 3 hours, the solvent was distilled off. Ether was added to the residue for crystallization and the resulting crystals were collected by filtration, whereby the title compound (307 mg, 76%) was obtained as a colorless solid.

[0869]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.20(4H,m), 3.30-3.90(4H,m), 7.47(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 7.89(2H,d,J=8.3Hz), 8.19(1H,d,J=8.8Hz), 8.22(1H,d,J=1.0Hz), 8.25-8.30(2H,m), 8.50(1H,m), 9.22(1H,d,J=1.0Hz).

MS (FAB) m/z: 481 [$(M+H)^+$, Cl^{35}], 483 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}ClN_4O_3S \cdot HCl \cdot 0.4H_2O$

Calculated: C, 54.94; H, 4.38; N, 10.68; Cl, 13.52; S, 6.11.

Found: C, 54.98; H, 4.29; N, 10.62; Cl, 13.56; S, 6.14.

[0870]

[Example 11]

1-[4-(2-Aminoimidazol-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-[2-aminoimidazol-4-yl]benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0871]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.20(4H,m), 3.30-3.90(4H,m), 7.39(2H,d,J=8.3Hz), 7.47(1H,s), 7.49(2H,br s), 7.67(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.5Hz), 7.82(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,br s).

MS (FAB) m/z: 496 [$(M+H)^+$, Cl^{35}], 498 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{22}N_5O_3ClS \cdot HCl$

Calculated: C, 54.14; H, 4.35; N, 13.15; Cl, 13.32; S, 6.02.

Found: C, 53.94; H, 4.39; N, 12.82; Cl, 13.27; S, 6.07.

[0872]

[Example 12]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In a mixed solvent of benzene (10 ml) and methanol (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (300 mg) obtained in Example 1 was dissolved at room temperature, followed by the addition of methyl iodide (1 ml). To the resulting mixture, the same amount of methyl iodide was added three times at intervals of 24 hours, followed by heating under reflux for 4 days. The reaction mixture was distilled under reduced pressure and the residue was washed with methanol, collected by filtration and dried, whereby the title compound (229 mg, 58%) was obtained as a yellow solid.

[0873]

^{1}H-NMR (DMSO-d_6) δ: 3.03(2H,br s), 3.13(2H,br s), 3.43(2H,br s), 3.75(2H,br s), 4.34(3H,s), 7.59(2H,d,J=8.8Hz), 7.74(1H,dd,J=8.8,2.4Hz), 7.85(1H,dd,J=8.8,2.0Hz), 8.08(2H,d,J=8.8Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.45-8.55(3H,m), 9.03(2H,d,J=6.8Hz).

Elementary analysis for $C_{27}H_{25}N_3O_3ClIS\cdot H_2O$

Calculated: C, 49.74; H, 4.17; N, 6.45.

Found: C, 49.60; H, 4.09; N, 6.23.

[0874]

[Example 13]

3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine, which had been obtained in Example 5, as a raw material, whereby the title compound was obtained.

[0875]

^{1}H-NMR ($CDCl_3$) δ: 2.90-3.40(4H,m), 3.40-4.20(4H,m), 7.50-7.60(1H,m), 7.40-7.45(3H,m), 7.54(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.90-8.00(3H,m), 8.22(1H,d,J=5.9Hz), 8.31(1H,d,J=2.0Hz), 8.43(1H,br s).

MS (FAB) m/z: 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}N_3O_4ClS\cdot H_2O$

Calculated: C, 59.37; H, 4.60; N, 7.99; Cl, 6.74; S, 6.10.

Found: C, 59.48; H, 4.69; N, 7.74; Cl, 6.73; S, 6.07.

[0876]

[Example 14]

1-[2-Carboxy-4-(pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (50 ml), 1-[2-tert-butoxycarbonyl-4-(pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (250 mg) was dissolved, followed by the dropwise addition of trifluoroacetic acid (50 ml) under ice cooling. After stirring at room temperature for 5 hours, the solvent was distilled off. The residue was dissolved in methanol and the resulting solution was allowed to stand in a refrigerator for one day. The colorless solid so precipitated was collected by filtration and dried, whereby the title compound (550 mg, 28%) was obtained as a colorless solid.

[0877]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.40(6H,m), 3.65-3.75(2H,m), 7.41(1H,d,J=7.8Hz), 7.70-7.75(3H,m), 7.82(1H,dd,J=8.8,2.0Hz), 8.00(1H,dd,J=7.8,1.5Hz), 8.15-8.30(4H,m), 8.50(1H,br s), 8.67(2H,d,J=5.9Hz), 13.29(1H,br s).

MS (FAB) m/z: 536 [$(M+H)^+$, Cl^{35}], 538 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{22}ClN_3O_5S \cdot 0.5H_2O$

Calculated: C, 59.50; H, 4.25; N, 7.71; Cl, 6.50; S, 5.88.

Found: C, 59.54; H, 4.30; N, 7.37; Cl, 6.35; S, 5.89.

[0878]

[Example 15]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiophen-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 5-(pyridin-4-yl)thiophene-2-carboxylic acid hydrochloride obtained in Referential Example 28 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0879]

^{1}H-NMR (DMSO-d_6) δ: 3.11(4H,br s), 3.74(4H,br s), 7.52(1H,d,J=3.9Hz), 7.73(1H,dd,J=8.8,2.5Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.03(1H,d,J=3.9Hz), 8.10-8.15(2H,m), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.51(1H,s), 8.88(2H,d,J=6.8Hz).

MS (FAB) m/z: 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl \cdot H_2O$

Calculated: C, 52.17; H, 4.20; N, 7.61; Cl, 12.83; S, 11.61.

Found: C, 52.04; H, 4.22; N, 7.22; Cl, 12.74; S, 11.57.

[0880]

[Example 16]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)furan-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 5-(pyridin-4-yl)furan-2-carboxylic acid hydrochloride

obtained in Referential Example 29 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0881]

^{1}H-NMR (DMSO-d_6) δ: 3.13(4H,br s), 3.30-4.00(4H,m), 7.21(1H,d,J=3.9Hz), 7.71(1H,d,J=8.8Hz), 7.75-7.80(1H,m), 7.83(1H,d,J=8.8 Hz), 8.10-8.30(5H,m), 8.51(1H,s), 8.85-8.90(2H,m).

MS (FAB) m/z: 482 [$(M+H)^+$, Cl^{35}], 484 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot H_2O$

Calculated: C, 53.74; H, 4.32; N, 7.83; Cl, 13.22; S, 5.98.

Found: C, 53.51; H, 4.36; N, 7.57; Cl, 13.21; S, 5.97.

[0882]

[Example 17]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-(pyridin-2-yl)benzoic acid hydrochloride obtained in Referential Example 30 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0883]

^{1}H-NMR (DMSO-d_6) δ: 3.07(4H,br), 3.60-4.00(4H,br), 7.46(3H,br), 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 7.94-8.05(2H,br), 8.08(2H,d,J=8.8Hz), 8.18(1H,d,J=8.8Hz),

8.28(2H,d,J=8.8Hz), 8.50(1H,s), 8.70(1H,br).

MS (FAB) m/z: 492 [(M+H)$^+$, Cl^{35}], 494 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}ClN_3O_3S \cdot 0.9HCl \cdot H_2O$

Calculated: C, 57.53; H, 4.62; Cl, 12.41; N, 7.74; S, 5.91.

Found: C, 57.55; H, 4.52; Cl, 12.64; N, 7.61; S, 6.03.

[0884]

[Example 18]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 17, a reaction was conducted using 4-(2-pyridyl)benzoic acid hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0885]

^{1}H-NMR (DMSO-d_6) δ: 3.19(4H,br), 3.46(2H,br), 3.75(2H,br), 7.36(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.50-7.58(1H,br), 7.53(2H,d,J=7.8Hz), 7.57(2H,d,J=7.8Hz), 7.82(2H,d,J=7.8Hz), 8.13(2H,m), 8.15(2H,d,J=7.8Hz), 8.75(1H,d,J=4.9Hz).

MS (FAB) m/z: 468 [(M+H)$^+$, Cl^{35}], 470 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{22}ClN_3O_3S \cdot HCl \cdot 0.3EtOH \cdot 0.3H_2O$

Calculated: C, 56.42 H, 4.89; Cl, 13.54; N, 8.02; S, 6.12.

Found: C, 56.51 H, 4.83; Cl, 13.46; N, 8.10; S, 5.99.

[0886]

[Example 19]

2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-

yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained in Example 17, as a raw material, whereby the title compound was obtained.

[0887]

^{1}H-NMR ($CDCl_3$) δ: 3.11(4H,br), 3.63(2H,br), 3.87(2H,br), 7.27(1H,m), 7.33(1H,t,J=8.8Hz), 7.39-7.41(1H,br), 7.40(2H,d,J=7.8Hz), 7.60(1H,d,J=8.8Hz), 7.77(1H,d,J=8.8Hz), 7.83(2H,d,J=7.8Hz), 7.93(1H,d,J=3.8Hz), 7.94(1H,s), 8.31(1H,s), 8.33(1H,d,J=5.9Hz).

MS (FAB) m/z: 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}ClN_3O_4S$

Calculated: C, 61.47; H, 4.37; Cl, 6.98; N, 8.27; S, 6.31.

Found: C, 61.32; H, 4.46; Cl, 7.21; N, 8.13; S, 6.02.

[0880]

[Example 20]

2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In the same manner as in Example 12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained in Example 17, as a raw material, whereby the title compound was obtained.

[0889]

^{1}H-NMR (DMSO-d_6) δ: 2.93-3.23(4H,br), 3.54(2H,br), 3.82(2H,br), 4.30(3H,s), 7.50(2H,d,J=8.8Hz), 7.53(1H,m), 7.70(2H,d,J=8.8Hz), 7.70(1H,br), 7.84-7.92(4H,m), 8.15(1H,t,J=6.8Hz), 8.26(1H,s), 8.52(1H,t,J=6.8Hz), 9.29(1H,d,J=5.9Hz).

Elementary analysis for $C_{27}H_{25}ClIN_3O_3S \cdot 1.6H_2O$

Calculated: C, 48.93; H, 4.29; N, 6.34.

Found: C, 48.81; H, 4.06; N, 6.31.

[0890]

[Example 21]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2,4-diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0891]

^{1}H-NMR (DMSO-d_6) δ: 3.14(4H,br), 3.45(2H,br s), 3,73(2H,br s), 6,36(1H,s), 7,54(2H,d,J=7.8Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz), 7.83(1H,s), 7.84(2H,d,J=7.8Hz), 8.18(1H,J=8.8Hz), 8.18-8.35(3H,br), 8.27(1H,s), 8.28(1H,d,J=8.8Hz), 8.50(1H,s), 12.64(1H,br s).

MS (FAB) m/z: 523 [$(M+H)^+$, Cl^{35}], 525 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_6O_3S \cdot HCl \cdot 1.4H_2O$

Calculated: C, 51.36; H, 4.62; Cl, 12.13; N, 14.37; S, 5.48.

Found: C, 51.38; H, 4.54; Cl, 12.24; N, 14.23; S, 5.55.

[0892]

[Example 22]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(2,4-diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 21, a reaction was conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl)piperazine hydrochloride obtained in Referential Example 31 as raw materials, whereby the title compound was obtained.

[0893]

^{1}H-NMR (DMSO-d_6) δ: 3.18(4H,br), 3.43(2H,br), 3.76(2H,br), 4.0(2H,br), 6.37(1H,s), 7.84(2H,d,J=15.6Hz), 7.44(1H,J=15.6Hz), 7.53(2H,d,J=8.8Hz), 7.63(2H,d,J=8.8Hz), 7.82(1H,d,J=8.8Hz), 7.88(1H,d,J=8.8Hz), 8.23(1H,br s), 8.32(1H,br s), 12.58(1H,br s).

MS (FAB) m/z: 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{23}ClN_6O_3S\cdot1.2HCl\cdot1.4H_2O$

Calculated: C, 48.64; H, 4.79; Cl, 13.73; N, 14.80; S, 5.65.

Found: C, 48.46; H, 4.56; Cl, 13.53; N, 14.54; S, 5.72.

[0894]

[Example 23]

2-[4-[[4-(E)-4-Chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 1, a reaction was conducted using 2-[4-[(1-piperazyl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (E)-4-chlorostyrylsulfonyl chloride (WO96/10022) as raw materials, whereby the title compound was obtained.

[0895]

^{1}H-NMR ($CDCl_3$) δ: 3.10-3.40(4H,br), 3.66(2H,br), 3.89(2H,br), 6.65(1H,d,J=15.6Hz), 7.28(1H,m), 7.34(1H,t,J=7.8Hz), 7.39-7.48(6H,m), 7.50(2H,d,J=7.8Hz), 7.88(2H,d,J=7.8Hz), 8.34(1H,d,J=5.9Hz).

MS (FD) m/z: 483 (M^+, Cl^{35}), 485 (M^+, Cl^{37}).

Elementary analysis for $C_{24}H_{22}ClN_3O_4S \cdot 0.5H_2O$

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

Found: C, 58.49; H, 4.80; Cl, 7.29; N, 8.31; S, 6.34.

[0896]

[Example 24]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

Under ice cooling, piperazine (727 mg) was dissolved in dichloromethane (10 ml), followed by the addition of (E)-4-chlorostyrylsulfonyl chloride (WO96/10022) (500 mg) in portions. After stirring at room temperature for one hour, the reaction mixture was diluted with dichloromethane (100 ml), washed with a saturated aqueous solution of sodium bicarbonate, a 5% aqueous solution of citric acid, water and saturated saline and then dried over anhydrous magnesium sulfate. The residue

obtained by distilling off the solvent under reduced pressure was suspended in N,N-dimethylformamide (10 ml), followed by the addition of 4-(4-pyridyl)benzoic acid (420 mg) obtained in Referential Example 2 and N,N-dimethyl-4-aminopyridine (309 mg). Under ice cooling, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (405 mg) was added and the resulting mixture was stirred at room temperature for 68 hours. After concentration, the residue was purified by chromatography on a silica gel column (dichloromethane : methanol = 70:1). The colorless solid so obtained was recrystallized from a mixed solvent of ethyl acetate and hexane, followed by recrystallization from ethyl acetate to obtain colorless needle crystals (185 mg). To the filtrate, on the other hand, saturated hydrochloric acid - ethanol (4 ml) was added. After concentration, the residue was recrystallized from methanol - ethyl acetate, whereby the title compound (200 mg) was obtained as colorless needle crystals.

[0897]

^{1}H-NMR (DMSO-d_6) δ: 3.17(2H,br s), 3.23(2H,br s), 3.48(2H,br s), 3.77(2H,br s), 7.36(1H,d,J=15.3Hz), 7.44(1H,d,J=15.3Hz), 7.53(2H,d,J=8.8Hz),7.64(2H,d,J=8.3Hz), 7.82(2H,d,J=8.3Hz), 8.06(2H,d,J=8.8Hz), 8.32(2H,d,J=6.6Hz), 8.95(2H,d,J=6.6Hz).

MS (FAB) m/z: 468 [(M+H)$^+$, Cl^{35}], 470 [(M+H)$^+$, Cl^{37}].

Elementary analysis for

$C_{24}H_{22}ClN_3O_3S \cdot HCl \cdot 0.2H_2O \cdot 0.22CH_3CO_2CH_2CH_3$

Calculated: C, 56.66; H, 4.81; Cl, 13.44; N, 7.97; S, 6.08.

Found: C, 56.68; H, 4.79; Cl, 13.43; N, 8.04; S, 6.14.

[0898]

[Example 25]

4-[4-[[4-[(E)-4-Chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In the same manner as in Example 12, a reaction was conducted using 1-[(E)-4-chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine, which had been obtained in Example 24, as a raw material, whereby the title compound was obtained.

[0899]

^{1}H-NMR (DMSO-d_6) δ: 3.04-3.87(8H,br), 4.35(3H,s), 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.53(2H,d,J=8.3Hz), 7.67(2H,d,J=8.3Hz), 7.82(2H,d,J=8.8Hz), 8.13(2H,d,J=8.3Hz), 8.53(2H,d,J=6.8Hz), 9.05(2H,d,J=7.3Hz).

Elementary analysis for $C_{25}H_{25}ClIN_3O_3S \cdot 0.5H_2O$

Calculated: C, 48.52; H, 4.23; N, 6.79.

Found: C, 48.68; H, 4.13; N, 6.41.

[0900]

[Example 26]

3-[4-[[4-[(E)-4-Chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

After the protecting group was removed by the reaction as in Example 7, the reaction with (E)-4-chlorostyrylsulfonyl chloride (WO96/10022) was effected in the same manner as in

Example 23, whereby the title compound was obtained.

[0901]

^{1}H-NMR ($CDCl_3$) δ: 3.26(4H,br), 3.52-4.00(4H,br), 6.64(1H,d,J=15.6Hz), 7.45-7.52(7H,m), 7.52(2H,d,J=2.0Hz), 7.57(2H,d,J=2.0Hz), 8.22(1H,dt,J=6.3,1.6Hz), 8.44(1H,t,J=1.6Hz).

MS (FAB) m/z: 484 [$(M+H)^+$, Cl^{35}], 486 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{22}ClN_3O_3S\cdot 0.5H_2O$

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

Found: C, 58.49; H, 4.66; Cl, 7.40; N, 8.54; S, 6.56.

[0902]

[Example 27]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 17, a reaction was effected using 4-(3-pyridyl)benzoic acid hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0903]

^{1}H-NMR (DMSO-d_6) δ: 3.08-3.29(4H,br), 3.42-3.85(4H,br), 7.35(1H,d,J=15.6Hz), 7.43(1H,d,J=15.6Hz), 7.52(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 7.80-7.93(5H,m), 8.54(1H,d,J=6.8Hz), 8.78(1H,d,J=4.5Hz), 9.13(1H,d,J=2.0Hz).

MS (FAB) m/z: 468 [$(M+H)^+$, Cl^{35}], 470 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{22}ClN_3O_3S\cdot HCl\cdot 1.3H_2O$

Calculated: C, 54.61; H, 4.89; N, 7.96; Cl, 13.43; S, 6.07.

Found: C, 54.82; H, 4.80; N, 7.91; Cl, 13.14; S, 6.14.

[0904]

[Example 28]

3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In the same manner as in Example 12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine, which had been obtained in Example 5, as a raw material, whereby the title compound was obtained.

[0905]

^{1}H-NMR (DMSO-d_6) δ: 2.50-3.80(8H,m), 4.44(3H,s), 7.57(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.84(1H,dd,J=8.8,1.5Hz), 7.94(2H,d,J=8.3Hz), 8.10-8.30(4H,m), 8.51(1H,s), 8.90(1H,d,J=7.8Hz), 9.01(1H,d,J=5.9Hz), 9.45(1H,s).

MS (FAB) m/z: 506 [$(M+H)^+$, Cl^{35}], 508 [$(M+H)^+$, Cl^{37}].

[0906]

[Example 29]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 2-(hydroxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0907]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.40(8H,m), 7.25-7.40(3H,m), 7.70-7.80(1H,m), 7.80-7.90(1H,m), 8.15-8.25(3H,m), 8.25-8.35(2H,m), 8.50-8.60(1H,m), 8.91(2H,d,J=6.4Hz), 10.41(1H,br s).

MS (FAB) m/z: 535 [(M+H)$^+$, Cl^{35}], 537 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}ClN_3O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.96; H, 4.62; N, 7.26; Cl, 12.86; S, 5.54.

Found: C, 53.62; H, 4.58; N, 7.34; Cl, 13.10; S, 5.94.

[0908]

[Example 30]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 3-methoxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0909]

^{1}H-NMR (DMSO-d_6) δ: 3.00-4.00(8H,m), 3.81(3H,s), 7.08(1H,d,J=8.8Hz), 7.17(1H,s), 7.55(1H,d,J=8.8Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.3Hz), 8.04(2H,d,J=6.3Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.52(1H,s), 8.85(2H,d,J=6.3Hz).

MS (FAB) m/z: 522 [(M+H)$^+$, Cl^{35}], 524 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot 0.8HCl \cdot 1.7H_2O$

Calculated: C, 55.74; H, 4.89; N, 7.22; Cl, 10.97; S, 5.51.

Found: C, 55.59; H, 4.90; N, 7.23; Cl, 10.90; S, 5.52.

[0910]

[Example 31]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In dichloromethane (1 ml), boron tribromide (115 µl) was dissolved, followed by the dropwise addition of a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine, which had been obtained in Example 30, in dichloromethane (dichloromethane: 4 ml) at an external temperature of about -78°C. While heating gradually to room temperature, the resulting mixture was stirred for 23 hours. After dichloromethane and water were added to the reaction mixture and the resulting mixture was stirred for a while, sodium bicarbonate was added to make alkaline the reaction mixture and the organic layer was collected. The water layer was then extracted with dichloromethane. These organic layers were combined together, washed with saturated saline and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 3% methanol - dichloromethane). The crudely purified product so obtained was dissolved in tetrahydrofuran. Ethanol hydrochloride was added to the resulting solution to solidify the same. The resulting solid was collected by

filtration and then dissolved in a mixed solvent of water and methanol. After the removal of the insoluble matter by filtration, the filtrate was distilled under reduced pressure, whereby the title compound (36 mg, 30%) was obtained.

[0911]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.80(8H,m), 6.85-6.95(1H,m), 7.01(1H,d,J=1.4Hz), 7.49(1H,d,J=8.8Hz), 7.72(1H,dd,J=8.8,2.0Hz), 7.81(1H,dd,J=8.5,1.7Hz), 7.94(2H,d,J=6.4Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.51(1H,s), 8.75(2H,d,J=5.9Hz), 10.67(1H,s).

MS (FAB) m/z: 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}].

[0912]

[Example 32]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 7, a reaction was effected using 4-tert-butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine as a raw material and the protecting group was removed. The residue was then reacted with 4-(4-pyridyl)benzoic acid hydrochloride as in Example 4, whereby the title compound was obtained.

[0913]

^{1}H-NMR ($CDCl_3$) δ: 0.80-1.10(3H,m), 3.00-4.00(8H,m), 4.60-4.80(1H,m), 7.42(2H,d,J=7.8Hz), 7.47(2H,d,J=5.9Hz), 7.50-7.60(1H,m), 7.64(2H,d,J=8.3Hz), 7.70-7.80(1H,m), 7.85-

7.95(3H,m), 8.33(1H,s), 8.69(2H,s).

MS (FAB) m/z: 564 [$(M+H)^+$, Cl^{35}], 566 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_5S \cdot 0.3H_2O$

Calculated: C, 60.78; H, 4.70; N, 7.33; Cl, 6.80; S, 5.60.

Found: C, 60.84; H, 4.84; N, 6.98; Cl, 7.03; S, 5.70.

[0914]

[Example 33]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid

In the same manner as in Example 3, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine as a raw material.

^{1}H-NMR (DMSO-d_6) δ: 2.70-5.00(7H,m), 7.40-7.50(2H,m), 7.65-7.75(2H,m), 7.85-8.25(8H,m), 8.50-8.60(2H,m), 8.80-8.95(2H,m).

MS (FAB) m/z: 536 [$(M+H)^+$, Cl^{35}], 538 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{22}ClN_3O_5S \cdot 0.3HCl \cdot H_2O$

Calculated: C, 57.40; H, 4.34; N, 7.44; Cl, 8.16; S, 5.68.

Found: C, 57.16; H, 4.35; N, 7.36; Cl, 7.92; S, 6.08.

[0915]

[Example 34]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine

In the same manner as in Example 2, a reaction was effected,

whereby the title compound was obtained.

[0916]

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30(3H,m), 2.60-4.60(8H,m), 5.33(1H,br), 7.40-7.55(3H,m), 7.70-7.85(4H,m), 8.05-8.10(1H,m), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50-8.65(2H,m), 8.91(1H,s).

MS (FAB) m/z: 564 [$(M+H)^+$, Cl^{35}], 566 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_5S \cdot 0.1HCl \cdot 0.5H_2O$

Calculated: C, 60.40; H, 4.74; N, 7.29; Cl, 6.76; S, 5.56.

Found: C, 60.67; H, 4.61; N, 7.30; Cl, 6.89; S, 5.51.

[0917]

[Example 35]

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 3, with 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine (426 mg) as a raw material, a crude product was obtained by the hydrolysis of the ester, followed by suspension in N,N-dimethylformamide (35 ml). Under ice cooling, di-tert-butyl dicarbonate (646 mg), pyridine (370 μl) and ammonium bicarbonate (196 mg) were added to the resulting suspension. The resulting mixture was stirred at room temperature for 19 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (4% methanol - dichloromethane) and the eluate was dissolved in

tetrahydrofuran. Ethanol hydrochloride was added to the resulting solution to solidify the same. The resulting solid was collected by filtration and dissolved in a mixed solvent of water and methanol. The insoluble matter was filtered off and the filtrate was distilled under reduced pressure, whereby the title compound (302 mg, 65%) was obtained.

[0918]

^{1}H-NMR (DMSO-d_6) δ: 2.30-4.50(6H,m), 5.08(1H,br), 7.40-7.60(2H,m), 7.65-7.85(3H,m), 7.92(2H,d,J=7.8Hz), 8.00-8.10(1H,m), 8.20(2H,d,J=8.8Hz), 8.25-8.35(2H,m), 8.49(1H,s), 8.80(1H,d,J=7.8Hz), 8.88(1H,d,J=5.4Hz), 9.25(1H,s).

MS (FAB) m/z: 535 [$(M+H)^+$, Cl^{35}], 537 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{23}ClN_4O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.54; H, 4.58; N, 9.25; Cl, 12.29; S, 5.29.

Found: C, 53.36; H, 4.71; N, 9.07; Cl, 12.17; S, 5.50.

[0919]

[Example 36]

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 35, the title compound was obtained using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine as a raw material.

[0920]

^{1}H-NMR (DMSO-d_6) δ: 2.30-2.70(2H,m), 3.20-3.80(2H,m), 4.10-

4.50(2H,m), 5.07(1H,br s), 7.40-7.55(2H,m), 7.60-7.65(1H,m), 7.67(1H,s), 7.72(1H,dd,J=8.8,2.4Hz), 7.78(1H,dd,J=8.8,2.4Hz), 8.04(2H,d,J=8.8Hz), 8.20(1H,d,J=8.8Hz), 8.25-8.35(4H,m), 8.49(1H,s), 8.95(2H,d,J=5.4Hz).

MS (FAB) m/z: 535 [$(M+H)^+$, Cl^{35}], 537 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{23}ClN_4O_4S \cdot HCl \cdot 1.8H_2O$

Calculated: C, 53.70; H, 4.61; N, 9.28; Cl, 11.74; S, 5.31.

Found: C, 53.87; H, 4.40; N, 8.89; Cl, 11.81; S, 5.23.

[0921]

[Example 37]

4-[4-[[2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-pyridin-4-yl)benzoyl]piperazine as a raw material, whereby the title compound was obtained.

[0922]

^{1}H-NMR (DMSO-d_6) δ: 2.30-4.50(6H,m), 5.04(1H,br), 7.30-7.90(10H,m), 8.10-8.30(5H,m), 8.48(1H,s).

MS (FAB) m/z: 551 [$(M+H)^+$, Cl^{35}], 553 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{23}ClN_4O_5S \cdot 0.8H_2O$

Calculated: C, 57.35; H, 4.39; N, 9.91; Cl, 6.27; S, 5.67.

Found: C, 57.64; H, 4.50; N, 9.48; Cl, 6.37; S, 5.71.

[0923]

[Example 38]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 37, a reaction was conducted, whereby the title compound was obtained.

[0924]

^{1}H-NMR ($CDCl_3$) δ: 1.30-1.40(3H,m), 2.30-4.70(8H,m), 5.47(1H,br s), 7.40-7.80(8H,m), 7.92(1H,s), 7.94(2H,s), 8.26(2H,d,J=6.8Hz), 8.48(1H,s).

MS (FAB) m/z: 580 [$(M+H)^+$, Cl^{35}], 582 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_6S \cdot 1.3H_2O$

Calculated: C, 57.72; H, 4.78; N, 6.96; Cl, 5.87; S, 5.31.

Found: C, 57.99; H, 4.75; N, 6.56; Cl, 5.98; S, 5.43.

[0925]

[Example 39]

4-[4-[[2-Carboxy-4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 3, the title compound was obtained.

[0926]

^{1}H-NMR ($CDCl_3$) δ: 2.30-4.50(6H,m), 5.22(1H,br s), 7.35-7.50(2H,m), 7.70-7.90(6H,m), 8.19(1H,d,J=8.8Hz), 8.25-8.30(4H,m), 8.53(1H,s), 13.42(1H,br).

Elementary analysis for $C_{27}H_{22}ClN_3O_6S \cdot 0.2HCl \cdot 1.7H_2O$

Calculated: C, 54.97; H, 4.37; N, 7.12; Cl, 7.21; S, 5.44.

Found: C, 55.07; H, 4.40; N, 6.82; Cl, 7.16; S, 5.47.

[0927]

[Example 40]

2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-[1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride, and

2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-[1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

[0928]

In the same manner as in Example 35, a reaction was conducted, whereby the title compounds were obtained.

2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-[1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

^{1}H-NMR (CD_3OD) δ: 2.80-4.80(6H,m), 5.32(1H,br), 7.04(1H,d,J=15.6Hz), 7.40-7.50(3H,m), 7.60-7.80(4H,m), 7.95-8.05(2H,m), 8.20(2H,br), 8.81(2H,br).

MS (FAB) m/z: 511 [$(M+H)^+$, Cl^{35}], 513 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_4O_4S \cdot 0.9HCl \cdot 1.8H_2O$

Calculated: C, 52.11; H, 4.81; N, 9.72; Cl, 11.69.

Found: C, 52.28; H, 4.83; N, 9.44; Cl, 11.51.

[0929]

2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

^{1}H-NMR (CD_3OD) δ: 1.10-1.20(3H,m), 2.95-4.70(6H,m), 5.34(1H,br), 7.38(4H,s), 7.65-7.85(2H,m), 8.05-8.15(2H,m), 8.40-8.50(2H,m), 8.91(2H,d,J=5.9Hz).

MS (FAB) m/z: 557 [(M+H)$^+$, Cl^{35}], 559 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{29}ClN_4O_5S \cdot HCl \cdot 2.5H_2O$

Calculated: C, 50.78; H, 5.52; N, 8.77; Cl, 11.10; S, 5.02.

Found: C, 50.61; H, 5.38; N, 8.68; Cl, 11.27; S, 5.07.

[0930]

[Example 41]

1-[trans-4-(Aminomethyl)cyclohexylmethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was conducted, whereby the title compound was obtained.

[0931]

^{1}H-NMR (DMSO-d_6) δ: 0.80-1.00(4H,m), 1.48(1H,m), 1.60-1.90(5H,m), 2.60(2H,m), 2.90-3.10(4H,m), 3.14(2H,m), 3.52(2H,m), 3.77(2H,m), 7.75(1H,dd,J=8.8,2.0Hz), 7.85(1H,d,J=8.8Hz), 7.99(3H,br), 8.21(1H,d,J=8.8Hz), 8.30-8.40(2H,m), 8.56(1H,s), 10.46(1H,br).

MS (FAB) m/z: 436 [(M+H)$^+$, Cl^{35}], 438 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{30}ClN_3O_2S \cdot 2HCl \cdot 3/4H_2O$

Calculated: C, 50.58; H, 6.46; N, 8.04; Cl, 20.36; S, 6.14.

Found: C, 50.74; H, 6.48; N, 7.76; Cl, 20.09; S, 6.19.

[0932]

[Example 42]

1-[trans-4-(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was

obtained using 1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0933]

^{1}H-NMR (DMSO-d_6) δ: 0.90-1.00(2H,m), 1.20-1.40(2H,m), 1.48(1H,m), 1.50-1.70(2H,m), 1.70-1.90(2H,m), 2.44(1H,m), 2.59(2H,m), 2.96(4H,m), 3.55(4H,m), 7.72(1H,dd,J=8.8,2.0Hz), 7.81(1H,d,J=8.3Hz), 7.90(3H,br), 8.16(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8,49(1H,s).

MS (FAB) m/z: 450 [$(M+H)^+$, Cl^{35}], 452 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{28}ClN_3O_3S\cdot0.9HCl\cdot1.5H_2O$

Calculated: C, 51.83; H, 6.31; N, 8.24; Cl, 13.21; S, 6.29.

Found: C, 51.63; H, 6.22; N, 7.97; Cl, 13.32; S, 6.17.

[0934]

[Example 43]

1-[N-[trans-4-(Aminomethyl)cyclohexylcarbonyl]glycyl]]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, a reaction was conducted using 1-[N-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycyl]]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0935]

^{1}H-NMR (DMSO-d_6) δ: 0.80-1.00(2H,m), 1.20-1.40(2H,m), 1.50(1H,m), 1.60-1.80(4H,m), 2.10(1H,m), 2.62(2H,m), 2.90-

3.10(4H,m), 3.40-3.60(4H,m), 3.83(2H,d,J=5.4Hz), 7.70-7.90(3H,m), 7.93(3H,br), 8.17(1H,d,J=8.3Hz), 8.20-8.30(2H,m), 8.49(1H,s).

MS (FAB) m/z: 507 [$(M+H)^+$, Cl^{35}], 509 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{31}ClN_4O_4S \cdot HCl$

Calculated: C, 53.04; H, 5.93; N, 10.31; Cl, 13.05; S, 5.90.

Found: C, 52.90; H, 5.98; N, 10.29; Cl, 12.98; S, 5.91.

[0936]

[Example 44]

1-[trans-4-(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a raw material.

[0937]

^{1}H-NMR (DMSO-d_6) δ: 0.90-1.10(2H,m), 1.30-1.50(2H,m), 1.50-1.90(7H,m), 2.40-2.80(3H,m), 3.20-3.70(8H,m), 7.60-7.70(1H,m), 7.80-8.00(4H,m), 8.10-8.20(1H,m), 8.20-8.30(2H,m), 8.52 and 8.53(1H, each s).

MS (FAB) m/z: 464 [$(M+H)^+$, Cl^{35}], 466 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{30}ClN_3O_3S \cdot HCl$

Calculated: C, 55.20; H, 6.24; N, 8.40; Cl, 14.17; S, 6.41.

Found: C, 55.42; H, 6.18; N, 8.26; Cl, 14.11; S, 6.53.

[0938]

[Example 45]

1-[4-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-(N-tert-butoxycarbonylaminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0939]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.20(4H,br), 3.30-3.80(4H,br), 4.03(2H,s), 7.37(2H,d,J=7.3Hz), 7.50(2H,d,J=7.3Hz), 7.72(1H,d,J=8.8Hz), 7.82(1H,d,J=8.8Hz), 8.18(1H,d,J=8.8Hz), 8.20-8.40(2H,m), 8.43(3H,br), 8,49(1H,s).

MS (FAB) m/z: 444 [$(M+H)^+$, Cl^{35}], 446 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{22}ClN_3O_3S \cdot HCl \cdot H_2O$

Calculated: C, 53.02; H, 5.06; N, 8.43; Cl, 14.23; S, 6.43.

Found: C, 53.06; H, 5.30; N, 8.32; Cl, 14.20; S, 6.44.

[0940]

[Example 46]

1-[3-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 3, the ester was hydrolyzed using methyl 3-(N-tert-butoxycarbonylaminomethyl)benzoate as a raw material. Reaction was then effected as in Example 4 or 7, whereby the title compound was obtained.

[0941]

^{1}H-NMR (DMSO-d_6) δ: 3.07(4H,br), 3.20-3.80(4H,br), 4.00(2H,s), 7.30-7.60(4H,m), 7.73(1H,d,J=8.8Hz), 7.83(1H,d,J=8.8Hz), 8.10-8.60(7H,m).

MS (FAB) m/z: 444 [$(M+H)^+$, Cl^{35}], 446 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{22}ClN_3O_3S \cdot HCl \cdot 1/4H_2O$

Calculated: C, 54.49; H, 4.88; N, 8.67; Cl, 14.62; S, 6.61.

Found: C, 54.64; H, 4.95; N, 8.52; Cl, 14.59; S, 6.70.

[0942]

[Example 47]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-[N-(1-pyrrolin-2-yl)aminomethyl]benzoyl]piperazine hydrochloride

In dimethylformamide (2 ml), 2-methoxy-1-pyrroline (35 mg) was dissolved, followed by the addition of 1-[3-(aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-ylsulfonyl]piperazine hydrochloride (0.10 g) and triethylamine (44 μl). The resulting mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with methanol, followed by the addition of 1N hydrochloric acid. The solvent was then distilled off under reduced pressure. The residue was purified by gel permeation chromatography ("Sephadex (trade name) LH-20", Ø 15 x 300 mm, methanol), followed by solidification in a mixed solvent of methanol and ether, whereby a colorless solid (0.11 g, 91%) was obtained.

[0943]

^{1}H-NMR (DMSO-d_6) δ: 2.04(2H,m), 2.81(2H,t,J=7.8Hz), 3.18(4H,br), 3.20-3.80(5H,m), 4.10(1H,br), 4.51(2H,d,J=5.9Hz), 7.30-7.50(4H,m), 7.72(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz), 8.18(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.50(1H,s), 10.01(1H,t,J=5.9Hz), 10.06(1H,s).

MS (FAB) m/z: 511 [$(M+H)^+$, Cl^{35}], 513 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{27}ClN_4O_3S \cdot HCl \cdot CH_3OH \cdot 4/5H_2$

Calculated: C, 54.60; H, 5.70; N, 9.43; Cl, 11.94; S, 5.40.

Found: C, 54.84; H, 5.47; N, 9.13; Cl, 11.86; S, 5.48.

[0944]

[Example 48]

1-[4-(2-Aminoethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-(2-(tert-butoxycarbonylamino)ethyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0945]

^{1}H-NMR (DMSO-d_6) δ: 2.90-3.20(8H,m), 3.40-3.90(4H,br), 7.28(4H,s), 7.72(1H,dd,J=8.8,2.4Hz), 7.81(1H,dd,J=8.8,2.0Hz), 8.02(3H,br), 8.17(1H,d,J=8,3Hz), 8.20-8.30(2H,m), 8.49(1H,s).

MS (FAB) m/z: 458 [$(M+H)^+$, Cl^{35}], 460 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{24}ClN_3O_3S \cdot HCl \cdot 1/2CH_3OH \cdot 1/2H_2O$

Calculated: C, 54.34; H, 5.43; N, 8.09; Cl, 13.65; S, 6.17.

Found: C, 54.43; H, 5.26; N, 7.92; Cl, 13.58; S, 6.24.

[0946]

[Example 49]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[4-[[(3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0947]

^{1}H-NMR (DMSO-d_6) δ: 2.05-2.25(2H,m), 3.00-3.10(4H,m), 3.20-3.70(8H,m), 5.16(1H,br s), 6.95(2H,d,J=8.8Hz), 7.31(2H,d,J=8.3Hz), 7.70-7.75(1H,m), 7.82(1H,dd,J=8.5,1.7Hz), 8.18(2H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.50(1H,s).

MS (FAB) m/z: 500 [$(M+H)^+$, Cl^{35}], 502[$(M+H)^+$, Cl^{37}].

[0948]

[Example 50]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[3-[[(3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[3-[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0949]

^{1}H-NMR (DMSO-d_6) δ: 2.00-2.20(2H,m), 2.95-3.15(4H,m), 3.20-3.80(8H,m), 5.11(1H,br s), 6.90-6.95(3H,m), 7.00-7.05(1H,m), 7.30-7.35(1H,m), 7.72(1H,dd,J=8.8,2.0Hz), 7.81(1H,dd,J=8.5,1.7Hz), 8.18(2H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,s).

MS (FAB) m/z: 500 [$(M+H)^+$, Cl^{35}], 502 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{26}ClN_3O_4S \cdot HCl \cdot H_2O$

Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.84; H, 5.19; N, 7.33; Cl, 12.72; S, 5.86.

[0950]

[Example 51]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[4-[[(3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-[[(3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0951]

^{1}H-NMR (DMSO-d_6) δ: 2.05-2.25(2H,m), 3.00-3.10(4H,m), 3.20-3.70(8H,m), 5.16(1H,br s), 6.96(2H,d,J=8.8Hz), 7.31(2H,d,J=8.8Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,1.5Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,s).

MS (FAB) m/z: 500 [$(M+H)^+$, Cl^{35}], 502 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{26}ClN_3O_4S \cdot 1.2HCl \cdot 0.8H_2O$

Calculated: C, 53.80; H, 5.20; N, 7.53; Cl, 13.97; S, 5.74.

Found: C, 53.84; H, 5.05; N, 7.51; Cl, 13.79; S, 5.74.

[0952]

[Example 52]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[3-[[(3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[3-[[(3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0953]

^{1}H-NMR (DMSO-d_6) δ: 2.00-2.20(2H,m), 2.95-3.15(4H,m), 3.20-3.80(8H,m), 5.11(1H,br s), 6.90-6.95(2H,m), 7.00-7.05(1H,m), 7.30-7.35(1H,m), 7.74(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,1,5Hz), 8.18(2H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,s).

MS (FAB) m/z: 500 [$(M+H)^+$, Cl^{35}], 502 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{26}ClN_3O_4S \cdot HCl \cdot H_2O$

Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.91; H, 5.14; N, 7.37; Cl, 12.62; S, 5.67.

[0954]

[Example 53]

1-[4-(2-Aminopyrimidin-5-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl]sulfonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-(2-amino-5-pyrimidyl)benzoic acid and 1-[(6-

chloronaphthalen-2-yl]sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0955]

^{1}H-NMR (DMSO-d_6) δ: 3.06(4H,br), 3.56 and (each 2H,br), 4.70-5.45(3H,br), 7.40(2H,d,J=8.8Hz), 7.67(2H,d,J=8.8Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz), 8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.28(1H,d,J=8.8Hz), 8.50(1H,s), 8.72(1H,s).

MS (FAB) m/z: 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{22}ClN_5O_3S \cdot 1.1HCl \cdot 0.7H_2O$

Calculated: C, 53.55; H, 4.40; Cl, 13.28; N, 12.49; S, 5.72.

Found: C, 53.59; H, 4.58; Cl, 13.02; N, 12.58; S, 5.89.

[0956]

[Example 54]

1-[(6-chloronaphthalen-2-yl]sulfonyl]-4-[(piperidin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[(1-tert-butoxycarbonylpiperidin-4-yl)acetyl]-4-[(6-chloronaphthalen-2-yl]sulfonyl]piperazine as a raw material.

[0957]

^{1}H-NMR (DMSO-d_6) δ: 1.25(2H,m), 1.71(2H,m), 1.87(1H,m), 2.20(2H,d,J=6.8Hz), 2.78(2H,br), 2.96(4H,br s), 3.14(2H,m), 3.52(4H,br s), 4.02(2H,br), 7.73(1H,dd,J=8.8,2.0Hz), 7.81(1H,d,J=8.8Hz), 8.17(1H,d,J=8.8Hz), 8.28(1H,d,J=8.8Hz),

8.26(1H,s), 8.50(1H,s), 8.54(1H,br), 8.75(1H,br).

MS (FAB) m/z: 436 [$(M+H)^+$, Cl^{35}], 438 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{21}H_{26}ClN_3O_3S \cdot 1.1HCl \cdot 1.1H_2O$

Calculated: C, 50.86; H, 5.96; Cl, 15.01; N, 8.47; S, 6.47.

Found: C, 51.07; H, 5.74; Cl, 14.75; N, 8.36; S, 6.50.

[0958]

[Example 55]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[3-(piperidin-4-yl)propionyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[3-(1-tert-butoxycarbonylpiperidin-4-yl)propionyl]-4-[(6-chloronaphthalen-2-yl]sulfonyl]piperazine as a raw material.

[0959]

^1H-NMR (CD_3OD)δ: 1.29(2H,m), 1.50(1H,m), 1.51(2H,m), 1.89(2H,m), 2.36(2H,m), 2.88(2H,m), 3.08(4H,m), 3.64(4H,m), 4.04(2H,br), 7.58(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 8.05(1H,d,J=8.8Hz), 8.06(1H,s), 8.09(1H,d,J=8.8Hz), 8.42(1H,s).

MS (FAB) m/z: 450 [$(M+H)^+$, Cl^{35}], 452 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{28}ClN_3O_3S \cdot 1.8HCl \cdot 0.9H_2O$

Calculated: C, 49.68; H, 5.99; Cl, 18.66; N, 7.90; S, 6.03.

Found: C, 49.45; H, 5.70; Cl, 18.63; N, 7.72; S, 6.04.

[0960]

[Example 56]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[(E)-3-(pyridin-3-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example 4, the title compound was obtained using (E)-3-(3-pyridyl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0961]

^{1}H-NMR (DMSO-d_6) δ: 3.03(4H,m), 3.69(2H,br), 3.85(2H,br), 7.51(2H,s), 7.70(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 7.89(1H,dd,J=7.8,5.4Hz), 8.16(1H,d,J=8.8Hz), 8.22(1H,d,J=2.0Hz), 8.26(1H,d,J=8.8Hz), 8.51(1H,s), 8.67(1H,d,J=7.8Hz), 8.77(1H,d,J=5.4Hz), 9.13(1H,s).

MS (FAB) m/z: 442 [(M+H)$^+$, Cl^{35}], 444 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{20}ClN_3O_3S \cdot HCl \cdot 1/4H_2O$

Calculated: C, 54.72; H, 4.49; N, 8.70; Cl, 14.68; S, 6.64.

Found: C, 54.81; H, 4.43; N, 8.54; Cl, 14.68; S, 6.74.

[0962]

[Example 57]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[(E)-3-(pyridin-4-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example 4, the title compound was obtained using (E)-3-(4-pyridyl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0963]

^{1}H-NMR (DMSO-d_6) δ: 3.03(4H,m), 3.68(2H,br), 3.82(2H,br), 5.76(1H,s), 7.48(1H,d,J=15.1Hz), 7.65(1H,d,J=15.1Hz), 7.72(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.11(2H,br s), 8.16(1H,d,J=8.8Hz), 8.24(1H,s), 8.27(1H,d,J=8.8Hz), 8.52(1H,s), 8.82(2H,d,J=5.9Hz).

MS (FAB) m/z: 442 [$(M+H)^+$, Cl^{35}], 444 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{20}ClN_3O_3S \cdot HCl \cdot 1/5H_2O$

Calculated: C, 54.82; H, 4.48; Cl, 14.71; N, 8.72; S, 6.65.

Found: C, 54.77; H, 4.41; Cl, 14.71; N, 8.50; S, 6.77.

[0964]

[Example 58]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[(pyridin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example 4, the title compound was obtained using 4-pyridylacetic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials.

[0965]

^{1}H-NMR (DMSO-d_6) δ: 2.99(2H,br), 3.04(2H,br), 3.57(2H,br), 3.62(2H,br), 4.00(2H,s), 7.71(2H,d,J=5.9Hz), 7.74(1H,dd,J=8.8,3.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.29(1H,d,J=8.8Hz), 8.53(1H,s), 8.72(2H,d,J=5.9Hz).

MS (FAB) m/z: 430 [$(M+H)^+$, Cl^{35}], 432 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{21}H_{20}ClN_3O_3S \cdot HCl \cdot 0.3H_2O$

Calculated: C, 53.46; H, 4.61; Cl, 15.03; N, 8.91; S, 6.80.

Found: C, 53.28; H, 4.49; Cl, 15.18; N, 8.91; S, 6.75.

[0966]

[Example 59]

1-[(6-Chloronaphthalen-2-yl]sulfonyl]-4-[4-[(3RS)-pyrrolidin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-[(3RS)-1-tert-butoxycarbonylpyrrolidin-3-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0967]

^{1}H-NMR (DMSO-d_6) δ: 1.85-1.95(1H,m), 2.30-2.40(1H,m), 3.00-3.90(13H,m), 7.72(1H,dd,J=8.6,2.2Hz), 7.80(1H,dd,J=8.8,2.0Hz), 7.29(2H,d,J=8.3Hz), 7.35(2H,d,J=8.3Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.49(1H,s).

MS (FAB) m/z: 484 [$(M+H)^+$, Cl^{35}], 486 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{26}ClN_3O_3S \cdot HCl \cdot 3/2H_2O$

Calculated: C, 54.84; H, 5.52; N, 7.67; Cl, 12.95; S, 5.86.

Found: C, 55.00; H, 5.53; N, 7.48; Cl, 13.23; S, 5.97.

[0968]

[Example 60]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[(1RS)-4-(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid and

1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0969]

^{1}H-NMR (DMSO-d_6) δ: 1.50-1.60(1H,m), 1.80-1.90(1H,m), 2.25-2.58(5H,m), 2.80-2.90(1H,m), 2.91-3.10(1H,m), 3.46-3.72(4H,m), 6.94(1H,br s), 7.71(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 7.96(2H,d,J=6.8Hz), 8.15(1H,J=8.8Hz), 8.24(1H,J=2.0Hz), 8.27(1H,J=8.8Hz), 8.50(1H,s), 8.76(2H,d,J=6.8Hz).

MS (FAB) m/z: 496 [$(M+H)^+$, Cl^{35}], 498 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{26}ClN_3O_3S \cdot HCl \cdot 1.3H_2O$

Calculated: C, 56.18; H, 5.37; Cl, 12.75; N, 7.56; S, 5.77.

Found: C, 56.03; H, 5.29; Cl, 12.67; N, 7.41; S, 5.77.

[0970]

[Example 61]

1-[(E)-4-Chlorostyrylsulfonyl]-4-[[(1RS)-4-(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid and 1-[(E)-4-chlorostyrylsulfonyl)piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0971]

^{1}H-NMR (DMSO-d_6) δ: 1.59-1.70(1H,m), 1.90-1.98(1H,m), 2.31-2.56(4H,m), 2.90-3.00(1H,m), 3.13(4H,br s), 3.50-3.63(4H,m),

6.98(1H,br s), 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.51(2H,d,J=8.3Hz), 7.80(1H,J=8.3Hz), 7.97(1H,J=6.8Hz), 8.77(1H,J=6.8Hz).

MS (FAB) m/z: 472 [$(M+H)^+$, Cl^{35}], 474 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{26}ClN_3O_3S \cdot 0.9HCl \cdot 2.3H_2O$

Calculated: C, 52.77; H, 5.81; Cl, 12.33; N, 7.69; S, 5.87.

Found: C, 52.61; H, 5.80; Cl, 12.54; N, 7.44; S, 6.05.

[0972]

[Example 62]

cis, trans-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using cis, trans-4-(4-pyridyl)cyclohexanecarboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0973]

MS (FAB) m/z: 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{28}ClN_3O_3S \cdot 1.3HCl \cdot 2H_2O$

Calculated: C, 53.71; H, 5.77; Cl, 14.02; N, 7.23; S, 5.51.

Found: C, 53.70; H, 5.70; Cl, 14.21; N, 7.13; S, 5.72.

[0974]

[Example 63]

cis, trans-1-[(E)-4-Chlorostyrylsulfonyl]-4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using cis, trans-4-(4-pyridyl)cyclohexanecarboxylic acid and 1-[(E)-4-chlorostyrylsulfonyl)piperazine hydrochloride as raw materials, whereby the title compound was obtained.

[0975]

MS (FAB) m/z: 474 [$(M+H)^+$, Cl^{35}], 476 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{28}ClN_3O_3S \cdot 1.2HCl \cdot 0.8H_2O$

Calculated: C, 54.17; H, 5.83; Cl, 14.66; N, 7.80; S, 6.03.

Found: C, 54.21; H, 6.20; Cl, 15.03; N, 7.51; S, 6.18.

[0976]

[Example 64]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(1,2,3,6-tetrahydropyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[0977]

^1H-NMR (DMSO-d_6) δ: 2.67(2H,br s), 3.05(4H,br), 3.30(2H,br s), 3.35-3.78(6H,m), 6.24(1H,br s), 7.32(2H,d,J=8.3Hz), 7.47(2H,d,J=8.3Hz), 7.71(1H,dd,J=8.8,2.0Hz), 7.81(1H,dd,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.22-8.28(2H,m), 8.49(1H,s), 9.25(2H,br s).

MS (FAB) m/z: 496 [$(M+H)^+$, Cl^{35}], 498 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{26}ClN_3O_3S \cdot HCl \cdot 2/5H_2O$

Calculated: C, 57.86; H, 5.19; Cl, 13.14; N, 7.79; S, 5.94.

Found: C, 57.91; H, 5.19; Cl, 12.91; N, 7.75; S, 5.78.

[0978]

[Example 65]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(piperidin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound was obtained using 1-[4-(1-tert-butoxycarbonylpiperidin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

^{1}H-NMR (DMSO-d_6) δ: 1.78-1.94(4H,m), 2.80-3.21(7H,m), 3.30-3.84(6H,m), 7.23(2H,d,J=8.3Hz), 7.28(2H,d,J=8.3Hz), 7.71(1H,dd,J=8.8,2.0Hz), 7.80(1H,dd,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.22-8.27(2H,m), 8.49(1H,s), 8.78-9.00(2H,m).

MS (FAB) m/z: 498 [(M+H)$^+$, Cl^{35}], 500 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{28}ClN_3O_3S \cdot HCl \cdot 3/5H_2O$

Calculated: C, 57.27; H, 5.58; Cl, 13.00; N, 7.71; S, 5.88.

Found: C, 57.23; H, 5.52; Cl, 12.90; N, 7.60; S, 5.83.

[0979]

[Example 66] (3RS)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[4-(pyridin-4-yl)benzoyl]pyrrolidine hydrochloride

In saturated ethanol hydrochloride, (3RS)-1-tert-butoxycarbonyl-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine was dissolved, followed by stirring

at room temperature for 8 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example 4, a reaction was conducted using the resulting residue and 4-(4-pyridyl)benzoic acid as raw materials, whereby the title compound was obtained.

[0980]

^{1}H-NMR (DMSO-d_6) δ: 1.70-2.10(2H,m), 3.00-3.65(4H,m), 3.75-3.90(1H,m), 7.50-8.40(13H,m), 8.95-9.05(2H,m).

MS (FAB) m/z: 492 [$(M+H)^+$, Cl^{35}], 494 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}ClN_3O_3S \cdot HCl \cdot 1.8H_2O$

Calculated: C, 55.68; H, 4.78; N, 7.49; Cl, 12.64; S, 5.72.

Found: C, 55.62; H, 4.94; N, 7.67; Cl, 12.76; S, 5.79.

[0981]

[Example 67]

(3RS)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[4-(pyridin-4-yl)benzamido]pyrrolidine hydrochloride

In saturated ethanol hydrochloride, (3RS)-1-tert-butoxycarbonyl-3-[4-(4-pyridyl)benzamido]pyrrolidine was dissolved, followed by stirring at room temperature for 4 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example 1, a reaction was conducted using the resulting residue and 6-chloro-2-naphthylsulfonyl chloride as raw materials, whereby the title compound was obtained as a hydrochloride.

[0982]

^{1}H-NMR (DMSO-d_6) δ: 1.90-2.10(2H,m), 3.00-3.60(4H,m), 4.15-4.25(1H,m), 7.57(1H,dd,J=8.8,2.0Hz), 7.73(2H,d,J=8.8Hz), 7.85(1H,dd,J=8.8,2.0Hz), 7.90(2H,d,J=8.8Hz), 7.95-8.05(2H,m), 8.18(1H,d,J=8.8Hz), 8.30-8.40(3H,m), 8.50(1H,s), 8.98(2H,d,J=6.4Hz).

MS (FAB) m/z: 492 [$(M+H)^+$, Cl^{35}], 494 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{22}ClN_3O_3S \cdot 0.8HCl \cdot 0.8H_2O$

Calculated: C, 58.31; H, 4.59; N, 7.85; Cl, 11.92; S, 5.99.

Found: C, 58.27; H, 4.68; N, 7.80; Cl, 11.94; S, 6.04.

[0983]

[Example 68]

1-[[(E)-2-(6-Chloropyridin-3-yl)ethylene]sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

To a suspension of 1-tert-butoxycarbonyl-4-[[(E)-2-(6-chloropyridin-3-yl)ethylene]sulfonyl]piperazine (390 mg) in ethanol (2 ml), saturated hydrochloric acid - ethanol (6 ml) was added, followed by stirring for 3 hours. The reaction mixture was concentrated and the residue was dissolved in N,N-dimethylformamide (10 ml). To the resulting solution, 4-(4-pyridyl)benzoic acid hydrochloride (262 mg) and N-methylmorpholine (1.00 ml) were added. Under ice cooling, 1H-benzotriazoyl-1-yloxytripyrrolidinophosphonium hexafluorophosphate was added, followed by stirring at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, washed successively with water, a saturated aqueous solution of sodium bicarbonate and saturated saline and

then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was recrystallized from a mixed solvent of dichloromethane and ethyl acetate. The resulting crystals were suspended in ethanol. Saturated hydrochloric acid - ethanol (6 ml) was added to the resulting suspension, followed by concentration into its hydrochloride. The resulting solid was recrystallized from ethanol, whereby the title compound (245 mg, 47%) was obtained as a colorless solid.

[0984]

^{1}H-NMR (DMSO-d_6) δ: 3.10-3.31(4H,br), 3.40-3.84(4H,br), 7.50(1H,d,J=15.9Hz), 7.52(1H,d,J=15.9Hz), 7.46(3H,d,J=8.3Hz), 8.06(2H,d,J=8.3Hz), 8.28-8.33(3H,m), 8.79(1H,d,J=2.0Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB) m/z: 469 [$(M+H)^+$, Cl^{35}], 471 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{21}ClN_4O_3S \cdot HCl \cdot 0.4H_2O$

Calculated: C, 53.89; H, 4.48; N, 10.93; Cl, 13.83; S, 6.26.

Found: C, 53.95; H, 4.47; N, 11.02; Cl, 13.91; S, 6.39.

[0985]

[Example 69]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Referential Example 7, a reaction was conducted using 1-(4-bromo-2-methylbenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material, whereby the title compound was obtained.

[0986]

^{1}H-NMR (DMSO-d_6) δ: 2.20(3H,s), 2.80-4.00(8H,m), 7.36(1H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.4Hz), 7.75-7.85(2H,m), 7.88(1H,s), 8.18(1H,d,J=8.8Hz), 8.20-8.30(4H,m), 8.50(1H,br s), 8.90(2H,d,J=6.8Hz).

MS (FAB) m/z: 506 [(M+H)$^+$, Cl^{35}], 508 [(M+H)$^+$, Cl^{37}].

[0987]

[Example 70]

4-[4-[4[-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-3-methylphenyl]pyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[2-methyl-4-(pyridin-4-yl)benzoyl]piperazine as a raw material, whereby the title compound was obtained.

[0988]

^{1}H-NMR ($CDCl_3$)δ: 2.27(3H,s), 2.80-4.20(8H,m), 7.16(1H,d,J=8.3Hz), 7.38(1H,J=8.3Hz), 7.41(1H,br s), 7.48(2H,d,J=6.8Hz), 7.61(1H,dd,J=8.8,1.5Hz), 7.75(1H,d,J=8.8Hz), 7.91-7.97(3H,m), 8.28(2H,d,J=6.8Hz), 8.31(1H,br s).

MS (FAB) m/z: 522 [(M+H)$^+$, Cl^{35}], 524 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot H_2O$

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

Found: C, 59.98; H, 4.89; Cl, 6.51; N, 7.48; S, 5.92.

[0989]

[Example 71]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 3-methyl-4-(4-pyridyl)benzoic acid hydrochloride as a raw material, whereby the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 2.27(3H,s), 3.08(4H,br), 3.47(2H,br), 3.72(2H,br), 7.26-7.37(3H,m), 7.73(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 7.86(2H,d,J=6.8Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.29(2H,m), 8.50(1H,br s), 8.87(2H,d,J=6.8Hz).

MS (FAB) m/z: 506 [$(M+H)^+$, Cl^{35}], 508 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_3S\cdot 0.9HCl\cdot 1.7H_2O$

Calculated: C, 56.95; H, 5.01; Cl, 11.83; N, 7.38; S, 5.63.

Found: C, 57.08; H, 5.04; Cl, 11.75; N, 7.37; S, 5.49.

[0990]

[Example 72]

4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-2-methylphenyl]pyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl piperazine as a raw material, whereby the title compound was obtained.

[0991]

^{1}H-NMR ($CDCl_3$) δ: 2.28(3H,s), 3.13(4H,br), 3.63(2H,br),

3.86(2H,br), 7.15-7.28(5H,m), 7.60(1H,d,J=8.8Hz), 7.76(1H,d,J=8.8Hz), 7.90-7.96(3H,m), 8.26(2H,d,J=6.8Hz), 8.31(1H,s).

MS (FAB) m/z: 522 [$(M+H)^+$, Cl^{35}], 524 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot H_2O$

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

Found: C, 59.71; H, 4.68; Cl, 6.87; N, 7.63; S, 5.91.

[0992]

[Example 73]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was conducted using 4-(2-methyl-4-pyridyl)benzoic acid hydrochloride as a raw material, whereby the title compound was obtained.

[0993]

^{1}H-NMR (DMSO-d_6) δ: 2.76(3H,s), 3.00-3.90(8H,m), 7.56(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.4Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.00(2H,d,J=8.3Hz), 8.14(1H,d,J=6.4Hz), 8.19(1H,d,J=8.8Hz), 8.22-8.29(3H,m), 8.51(1H,br s), 8.80(1H,d,J=6.4Hz).

MS (FAB) m/z: 506 [$(M+H)^+$, Cl^{35}], 508 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_3S \cdot HCl \cdot 2H_2O$

Calculated: C, 56.06; H, 5.05; Cl, 12.26; N, 7.26; S, 5.54.

Found: C, 55.84; H, 5.03; Cl, 12.26; N, 6.87; S, 5.54.

[0994]

[Example 74]

4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example 6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine as a raw material, whereby the title compound was obtained.

[0995]

^{1}H-NMR ($CDCl_3$) δ:2.58(3H,s), 3.13(4H,br), 3.65(2H,br), 3.84(2H,br), 7.34(1H,dd,J=6.8,2.4Hz), 7.41(2H,d,J=8.3Hz), 7.45(1H,d,J=2.4Hz), 7.56-7.62(3H,m), 7.76(1H,dd,J=8.8,2.0Hz), 7.91-7.96(3H,m), 8.28-8.32(2H,m).

MS (FAB) m/z: 522 [$(M+H)^+$, Cl^{35}], 524 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot H_2O \cdot 0.05CH_2Cl_2$

Calculated: C, 59.69; H, 4.83; Cl, 7.16; N, 7.72; S, 5.89.

Found: C, 59.47; H, 4.87; Cl, 6.98; N, 7.48; S, 6.10.

[0996]

[Example 75]

4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[2-(morpholin-4-yl)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 4, a reaction was conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide and 4-(2-aminoethyl)morpholine as raw materials, whereby the title compound was obtained.

[0997]

^1H-NMR ($CDCl_3$) δ: 2.22(4H,s), 2.35-2.80(6H,br), 3.20-3.90(3H,br), 3.74(4H,s), 4.20-4.60(1H,br), 5.25-5.50(1H,br), 6.80-7.20(1H,br), 7.45-7.70(7H,m), 7.76(1H,d,J=8.8Hz), 7.85-7.95(3H,m), 8.26(2H,d,J=6.9Hz), 8.32(1H,s).

MS (FAB) m/z: 664 [$(M+H)^+$, Cl^{35}], 666 [$(M+H)^+$, Cl^{37}].

[0998]

[Example 76]

4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[2-(dimethylamino)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 4, a reaction was conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide and 2-(dimethylamino)ethylamine as raw materials, whereby the title compound was obtained.

[0999]

^1H-NMR ($CDCl_3$) δ: 2.29(6H,s), 2.35-2.75(6H,br), 3.35-3.90(3H,br), 4.40-4.60(1H,br), 5.25-5.50(1H,br), 7.00-7.20(1H,br), 7.45-7.65(7H,m), 7.77(1H,dd,J=8.8,1.4Hz), 7.85-7.95(3H,m), 8.26(2H,d,J=7.3Hz), 8.34(1H,s).

MS (FAB) m/z: 622 [$(M+H)^+$, Cl^{35}], 624 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{31}H_{32}N_5O_5S \cdot 0.05CH_2Cl_2 \cdot 2H_2O$

Calculated: C, 56.30; H, 5.49; N, 10.57; Cl, 5.89; S, 4.84.

Found: C, 56.27; H, 5.37; N, 10.39; Cl, 6.01; S, 4.91.

[1000]

[Example 77]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine

In the same manner as in Referential Example 68, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-methoxycarbonylmethylpiperazine (723 g) and 4-(2-pyridyl)benzoic acid hydrochloride as raw materials, whereby the title compound was obtained.

[1001]

^{1}H-NMR (DMSO-d_6) δ: 2.30-4.50(11H,m), 5.06(1H,br s), 7.30-7.50(3H,m), 7.72(1H,dd,J=8.8,2.0Hz), 7.80-7.85(1H,m), 7.85-7.95(1H,m), 7.98(1H,d,J=7.8Hz), 8.10(2H,d,J=8.3Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.51(1H,s), 8.65-8.70(1H,m).

MS (FAB) m/z: 564 [$(M+H)^+$, Cl^{35}], 566 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_5S \cdot 1.1H_2O$

Calculated: C, 59.66; H, 4.87; N, 7.20; Cl, 6.07; S, 5.49.

Found: C, 59.53; H, 4.61; N, 7.05; Cl, 6.33; S, 5.70.

[1002]

[Example 78]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 3, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine

as a raw material, whereby the title compound was obtained.

[1003]

^{1}H-NMR (DMSO-d_6) δ: 2.30-4.50(8H,m), 5.05(1H,br s), 7.35-7.40(1H,m), 7.43(2H,d,J=8.8Hz), 7.72(1H,d,J=8.3Hz), 7.81(1H,d,J=8.8Hz), 7.85-7.90(1H,m), 7.97(1H,d,J=7.8Hz), 8.08(2H,d,J=8.8Hz), 8.17(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.49(1H,s), 8.65-8.70(1H,m).

MS (FAB) m/z: 550 [$(M+H)^+$, Cl^{35}], 552 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{24}ClN_3O_5S \cdot 0.4HCl \cdot 0.9H_2O$

Calculated: C, 57.90; H, 4.55; N, 7.23; Cl, 8.55; S, 5.52.

Found: C, 57.76; H, 4.26; N, 7.02; Cl, 8.44; S, 5.27.

[1004]

[Example 79]

2-Carbamoylmethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 35, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine as a raw material, whereby the title compound was obtained.

[1005]

^{1}H-NMR (DMSO-d_6) δ: 2.20-4.50(8H,m), 5.10(1H,br s), 6.96(2H,br s), 7.45-7.55(3H,m), 7.70-7.85(3H,m), 8.05-8.35(6H,m), 8.50(1H,s), 8.81(1H,d,J=4.9Hz).

MS (FAB) m/z: 549 [$(M+H)^+$, Cl^{35}], 551 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{25}ClN_4O_4S \cdot 1.3HCl \cdot 1.5H_2O$

Calculated: C, 53.94; H, 4.74; N, 8.99; Cl, 13.08; S, 5.14.

Found: C, 53.85; H, 4.87; N, 8.80; Cl, 13.19; S, 5.27.

[1006]

[Example 80]

1-[(Z)-4-Chloro-β-(2-hydroxyethan-1-yl)-β-styrylsulfonyl]-4-[4-(pyridin [Information cis 1] -2-yl)benzoyl]piperazine hydrochloride

Under ice cooling, 4-tert-butoxycarbonyl-1-[(Z)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-styrylsulfonyl]piperazine (355 mg) was dissolved in ethanol (3 ml), followed by the addition of saturated ethanol hydrochloride (6 ml). The resulting mixture was stirred at room temperature for 1 hour. After the reaction mixture was concentrated under reduced pressure, a reaction was effected in the same manner as in Example 4 by using the resulting residue, whereby the title compound (285 mg, 65%) was obtained.

[1007]

^{1}H-NMR (DMSO-d_6) δ: 2.58(2H,t,J=6.6Hz), 3.06(4H,br s), 3.15-3.60(4H,br), 3.68(2H,t,J=6.6Hz), 7.24(1H,s), 7.38(2H,d,J=8.6Hz), 7.40(2H,d,J=8.6Hz), 7.47-7.57(3H,m), 8.02-8.10(2H,m), 8.14(2H,d,J=8.3Hz), 8.74(1H,d,J=4.4Hz).

MS (FAB) m/z: 512 $(M+H)^+$.

[1008]

[Example 81]

1-[(E)-4-chloro-β-(2-hydroxyethan-1-yl)-β-styrylsulfonyl]-

4-[4-(pyridin [information cis 2] -2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 80, the title compound (240 mg, 74%) was obtained using 4-tert-butoxycarbonyl-1-[(E)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-styrylsulfonyl]piperazine (355 mg) as a raw material.

[1009]

^{1}H-NMR (DMSO-d_6) δ: 2.74(2H,t,J=7.3Hz), 3.27(4H,br s), 3.37-3.85(6H,m), 7.45(1H,s), 7.50-7.60(5H,m), 7.68(2H,d,J=8.3Hz), 8.06-8.17(4H,m), 8.75(1H,d,J=4.9Hz).

MS (FAB) m/z: 512 $(M+H)^+$.

Elementary analysis for $C_{26}H_{26}ClN_3O_4S \cdot 1.1HCl \cdot 0.8H_2O$

Calculated: C, 55.12; H, 5.11; N, 7.42; Cl, 13.14; S, 5.66.

Found: C, 55.22; H, 5.21; N, 7.20; Cl, 12.97; S, 5.66.

[1010]

In the same manner as in Example 7 or Example 1, the compounds shown in Examples 82 to 86 were synthesized.

[1011]

[Example 82]

1-[(1-Benzenesulfonyl-6-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1012]

^{1}H-NMR ($CDCl_3$) δ: 2.80-4.30(8H,br), 7.34(1H,d,J=8.5,1.7Hz), 7.43-7.62(9H,m), 7.69(2H,d,J=7.8Hz), 8.04(2H,d,J=7.8Hz), 8.33(1H,s), 8.70(2H,br s).

Elementary analysis for $C_{30}H_{25}ClN_4O_5S_2$

Calculated: C, 58.01; H, 4.06; Cl, 5.71; N, 9.02; S, 10.32.

Found: C, 58.34; H, 4.23; Cl, 5.78; N, 8.85; S, 9.96.

[1013]

[Example 83]

1-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]-4-[4-(piridin-4-yl)benzoyl]piperazine

[1014]

^{1}H-NMR (DMSO-d_6) δ: 2.67(3H,s), 3.15-3.31(4H,br), 3.37-3.84(4H,br), 7.58(1H,m), 7.65(1H,dd,J=8.8,2.0Hz), 7.92-8.03(2H,br), 8.13(1H,d,J=2.0Hz), 8.15-8.24(4H,m), 8.79-8.92(2H,br).

MS (FAB) m/z: 512 [(M+H)$^+$, Cl^{35}], 514 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{22}ClN_3O_3S_2HCl\cdot0.3H_2O$

Calculated: C, 54.21; H, 4.29; Cl, 12.80; N, 7.59; S, 11.58.

Found: C, 54.25; H, 4.25; Cl, 12.98; N, 7.52; S, 11.52.

[1015]

[Example 84]

1-[(1-Benzenesulfonyl-5-trimethylsilylethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1016]

^{1}H-NMR ($CDCl_3$) δ: 0.25(9H,s), 3.35-4.00(8H,m), 7.43(2H,t,J=8.1Hz), 7.47-7.64(7H,m), 7.64-7.74(3H,m), 8.00(2H,d,J=8.1Hz), 8.23(1H,d,J=8.8Hz), 8.71(2H,br s).

[1017]

[Example 85]

1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1018]

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.55(6H,br), 3.60-3.90(2H,br), 7.61(1H,dd,J=8.8,2.0Hz), 7.61(2H,d,J=8.8Hz), 7.68(1H,s), 7.84(1H,d,J=8.8Hz), 7.94(1H,d,J=2.0Hz), 8.05(2H,d,J=8.8Hz), 8.34(2H,d,J=5.9Hz), 8.95(2H,d,J=5.9Hz).

MS (FAB) m/z: 482 [(M+H)$^+$, Cl^{35}], 484 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.6H_2O$

Calculated: C, 54.47; H,4.23 ; Cl, 13.40; N, 7.94; S, 6.06.

Found: C, 54.48; H, 4.14; Cl, 13.41; N, 7.83; S, 6.17.

[1019]

[Example 86]

1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1020]

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.45(4H,br), 3.35-3.55(2H,br), 3.65-3.85(2H,br), 7.48(1H,d,J=8.8Hz), 7.59(2H,d,J=7.8Hz), 7.73(1H,s), 7.80-8.10(1H,m), 7.86(1H,d,J=8.8Hz), 7.98(1H,s), 8.04(2H,d,J=7.8Hz), 8.20-8.32(1/2H,m), 8.60-9.49(1H,br), 8.90-8.93(1/2H,m).

MS (FAB) m/z: 482 [(M+H)$^+$, Cl^{35}], 484 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.3H_2O$

Calculated: C, 55.03; H, 4.16; Cl, 13.54; N, 8.02; S, 6.12.

Found: C, 55.06; H, 4.12; Cl, 13.62; N, 7.89; S, 6.11.

[1021]

In the same manner as in Example 7 or Example 4, the compounds shown in Examples 87 to 93 were synthesized.

[1022]

[Example 87]

1-[(1-Benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1023]

^{1}H-NMR ($CDCl_3$) δ: 3.45-3.53(4H,br), 3.53-3.98(4H,br), 7.40-7.50(4H,m), 7.52-7.60(6H,m), 7.70(2H,d,J=8.3Hz), 8.01(2H,d,J=8.3Hz), 8.24(1H,d,J=9.3Hz), 8.73(2H,br).

MS (FAB) m/z: 621 [$(M+H)^+$, Cl^{35}], 623 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{30}H_{25}ClN_4O_5S_2 \cdot 0.1CH_2Cl_2$

Calculated: C, 57.42; H, 4.03; Cl, 6.76; N, 8.90; S, 10.19.

Found: C, 57.10; H, 4.35; Cl, 6.58; N, 8.80; S, 10.04.

[1024]

[Example 88]

1-[(1-Benzenesulfonyl-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1025]

^{1}H-NMR ($CDCl_3$) δ: 3.43-3.53(4H,br), 3.53-3.94(4H,br), 7.43(1H,t,J=7.6Hz), 7.40-7.46(2H,m), 7.48-7.65(10H,m), 7.69(2H,d,J=8.3Hz), 8.04(3H,m), 8.30(1H,d,J=8.3Hz), 8.69(2H,m).

MS (FAB) m/z: 587 $(M+H)^+$

Elementary analysis for $C_{30}H_{26}N_4O_5S_2 \cdot 0.5H_2O$

Calculated: C, 60.49; H, 4.57; N, 9.41; S, 10.77.

Found: C, 60.32; H, 4.73; N, 9.41; S, 10.43.

[1026]

[Example 89]

1-[(1-Benzensulfonyl-5-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

[1027]

^{1}H-NMR ($CDCl_3$) δ: 1.85-1.92(1H,m), 2.13-2.20(1H,m), 3.47-3.76(1H,m), 3.54-3.73(5H,m), 3.87-3.98(2H,m), 7.38-7.60(11H,m), 7.69(2H,d,J=6.8Hz), 8.02-8.08(2H,m), 8.18-8.23(1H,m), 8.69(2H,d,J=5.9Hz).

MS (FAB) m/z: 635 [$(M+H)^+$, Cl^{35}], 637 [$(M+H)^+$, Cl^{37}].

[1028]

[Example 90]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

[1029]

^{1}H-NMR (DMSO-d_6) δ: 2.92-3.26(4H,br), 3.35-3.78(4H,br), 7.03(1H,d,J=2.0Hz), 7.34(1H,dd,J=8.8,2.4Hz), 7.47-7.56(4H,m), 7.80(1H,d,J=2.0Hz), 8.02-8.16(4H,m), 8.73(1H,d,J=4.9Hz), 12.40(1H,s).

MS (FAB) m/z: 481 [$(M+H)^+$, Cl^{35}], 483 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}ClN_4O_3S \cdot 0.9HCl \cdot 1.6H_2O$

Calculated: C, 53.13; H, 4.66; Cl, 12.41; N, 10.33; S, 5.91.

Found: C, 53.29; H, 4.89; Cl, 12.40; N, 10.15; S, 5.92.

[1030]

[Example 91]

1-[(5-Chloro-1-methylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1031]

^{1}H-NMR ($CDCl_3$) δ: 3.09-3.45(4H,br), 3.49-4.03(4H,br), 3.70(3H,s), 7.08(1H,m), 7.33(1H,d,J=8.8Hz), 7.37(2H,d,J=7.8Hz), 7.44-7.53(3H,m), 7.64-7.69(3H,m), 8.69(2H,br).

MS (FAB) m/z: 495 [$(M+H)^+$, Cl^{35}], 497 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_4O_3S \cdot 0.1HCl \cdot 0.2H_2O$

Calculated: C, 56.12; H, 4.60; Cl, 13.25; N, 10.47; S, 5.99.

Found: C, 56.13; H, 4.54; Cl, 13.25; N, 10.40; S, 5.99.

[1032]

[Example 92]

1-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1033]

^{1}H-NMR (DMSO-d_6) δ: 1.30(3H,t,J=6.8Hz), 3.15-3.37(4H,br), 3.38-3.57(2H,br), 3.65-3.87(2H,br), 4.47(2H,q,J=6.8Hz), 7.17(1H,s), 7.41(1H,dd,J=8.8,2.0Hz), 7.63(2H,d,J=8.3Hz), 7.73(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.05(2H,d,J=8.3Hz), 8.31(2H,d,J=6.4Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB) m/z: 509 [$(M+H)^+$, Cl^{35}], 511 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{25}ClN_4O_3S \cdot 1.1HCl \cdot 1.2H_2O$

Calculated: C, 54.71; H, 5.03; Cl, 13.04; N, 9.82; S, 5.62.

Found: C, 54.51; H, 5.11; Cl, 13.06; N, 9.68; S, 5.71.

[1034]

[Example 93]

1-[(5-Chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1035]

^{1}H-NMR (DMSO-d_6) δ: 1.19(3H,t,J=6.8Hz), 3.00-3.29(4H,br), 3.30-3.85(4H,br), 4.14(2H,q,J=6.8Hz), 5.30(2H,s), 7.17-7.27(1H,m), 7.42(1H,d,J=8.8Hz), 7.59(2H,d,J=7.8Hz), 7.73(1H,d,J=8.8Hz), 7.84(1H,s), 8.01(2H,d,J=7.8Hz), 8.21(2H,d,J=6.3Hz), 8.88(2H,d,J=6.3Hz).

MS (FAB) m/z: 567 [$(M+H)^+$, Cl^{35}], 569 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{27}ClN_4O_5S \cdot 0.9HCl \cdot 0.5H_2O$

Calculated: C, 55.23; H, 4.78; Cl, 11.06; N, 9.20; S, 5.27.

Found: C, 54.91; H, 5.06; Cl, 10.78; N, 9.22; S, 5.45.

[1036]

In the same manner as in Example 4, the compounds shown in Examples 94 to 98 were synthesized.

[1037]

[Example 94]

1-[(5-Chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

[1038]

^{1}H-NMR (DMSO-d_6) δ: 3.28-3.90(8H,m), 7.61(2H,d,J=8.3Hz), 7.77(1H,dd,J=8.8,2.0Hz), 8.04(2H,d,J=8.8Hz), 8.28(2H,d,J=6.4Hz), 8.38(1H,d,J=8.8Hz), 8.43(1H,d,J=2.0Hz), 8.93(2H,d,J=6.4Hz).

MS (FAB) m/z: 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{19}ClN_4O_3S_2 \cdot HCl \cdot 0.6H_2O$

Calculated: C, 50.57; H, 3.91; Cl, 12.98; N, 10.26; S, 11.74.

Found: C, 50.72; H, 3.90; Cl, 13.22; N, 9.99; S, 11.35.

[1039]

[Example 95]

1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1040]

^{1}H-NMR (DMSO-d_6) δ: 3.28-3.90(8H,m), 7.55(2H,d,J=8.3Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.85-7.93(4H,m), 8.29(1H,d,J=8.8Hz), 8.50(1H,d,J=2.0Hz), 8.73(2H,d,J=6.4Hz).

MS (FAB) m/z: 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{19}ClN_4O_3S_2 \cdot 0.25HCl \cdot 0.5H_2O$

Calculated: C, 53.42; H, 3.95; Cl, 8.57; N, 10.83; S, 12.40.

Found: C, 53.22; H, 3.91; Cl, 8.41; N, 10.70; S, 12.59.

[1041]

[Example 96]

1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

[1042]

^{1}H-NMR (DMSO-d_6) δ: 3.02-4.00(8H,m), 7.51(2H,d,J=8.8Hz), 7.62(1H,dd,J=8.8,2.0Hz), 7.71(2H,d,J=5.4Hz), 7.82(2H,d,J=8.8Hz), 8.04(1H,s), 8.17(1H,d,J=2.0Hz), 8.19(1H,d,J=8.8Hz), 8.65(2H,d,J=5.4Hz).

MS (FAB) m/z: 498 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl$

Calculated: C, 53.93; H, 3.96; Cl, 13.27; N, 7.86; S, 12.00.

Found: C, 53.79; H, 4.07; Cl, 13.37; N, 7.70; S, 12.07.

[1043]

[Example 97]

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

[1044]

^{1}H-NMR (DMSO-d_6) δ: 3.03-3.88(8H,m), 7.56-7.61(3H,m), 8.02(2H,d,J=8.8Hz), 8.09(2H.d,J=8.8Hz), 8.29(2H.d,J=6.3Hz), 8.34(1H,d,J=2.0Hz), 8.94(2H,d,J=6.3Hz).

MS (FAB) m/z: 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl \cdot H_2O$

Calculated: C, 52.17; H, 4.20; Cl, 12.83; N, 7.61; S, 11.61.

Found: C, 52.18; H, 4.14; Cl, 12.84; N, 7.56; S, 11.70.

[1045]

[Example 98]

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

[1046]

^{1}H-NMR (DMSO-d_6) δ: 3.02-3.90(8H,m), 7.55(2H,d,J=8.3Hz), 7.58(1H,dd,J=8.3,1.5Hz), 7.62(1H,t,J=6.3Hz), 8.07-8.20(6H,m), 8.33(1H,d,J=1.5Hz), 8.77(1H,d,J=5.4Hz).

MS (FAB) m/z: 498 [(M+H)$^+$, Cl^{35}], 500 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl \cdot 0.8H_2O$

Calculated: C, 52.52; H, 4.15; Cl, 12.92; N, 7.66; S, 11.68.

Found: C, 52.69; H, 4.18; Cl, 12.63; N, 7.46; S, 11.68.

[1047]

[Example 99]

1-[(6-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (4.0 ml), 1-[(1-benzensulfonyl-6-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (380 mg) was dissolved, followed by the addition of methanol (4.0 ml) and potassium hydroxide (34.3 mg) at room temperature. The resulting mixture was stirred for 2 hours. To the reaction mixture, a saturated aqueous solution (30 ml) of ammonium chloride was added to make it weakly acidic. Then, a saturated aqueous solution (40 ml) of sodium bicarbonate was added to make the resulting mixture weakly alkaline. The resulting mixture was added with dichloromethane (30 ml). The organic layer collected by separation was extracted further with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure. The residue thus obtained was purified by

preparative thin-layer chromatography on a silica gel (dichloromethane : acetone : methanol = 20:2:1), followed by recrystallization from a mixed solvent of hexane and dichloromethane, whereby the title compound (157 mg, 53%) was obtained as a white solid.

[1048]

^{1}H-NMR ($CDCl_3$) δ: 2.70-4.20(8H,br), 7.02(1H,br s), 7.23(1H,dd,J=8.3,1.8Hz), 7.42-7.50(5H,m), 7.62-7.68(3H,m), 8.69(2H,d,J=5.9Hz), 8.78(1H,br s).

[1049]

In the same manner as in Example 99, the compounds shown in Examples 100 to 103 were synthesized.

[1050]

[Example 100]

1-[(Indol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1051]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.20(4H,br), 3.42-3.84(4H,br), 7.05(1H,s), 7.16(1H,t,J=7.3Hz), 7.33(1H,m), 7.50(3H,m), 7.72(2H,d,J=6.3Hz), 7.82(2H,d,J=7.8Hz), 7.65(2H,d,J=4.9Hz), 12.20(1H,s).

MS (FAB) m/z: 447 $(M+H)^+$

Elementary analysis for $C_{24}H_{22}N_4O_3S \cdot 0.2H_2O$

Calculated: C, 64.04; H, 5.02; N, 12.45; S, 7.12.

Found: C, 64.23; H, 5.30; N, 12.06; S, 7.07.

[1052]

[Example 101]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1053]

^{1}H-NMR (DMSO-d_6) δ: 2.94-3.25(4H,br), 3.30-3.41(4H,br), 7.03(1H,s), 7.33(1H,d,J=8.8Hz), 7.52(1H,d,J=8.8Hz), 7.59(2H,d,J=7.3Hz), 7.80(1H,s), 8.03(2H,d,J=7.3Hz), 8.33(2H,d,J=5.9Hz), 8.95(2H,d,J=5.9Hz), 12.5(1H,s).

MS (FAB) m/z: 481 [(M+H)$^+$, Cl^{35}], 483 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}ClN_4O_3S \cdot HCl \cdot 1.5H_2O$

Calculated: C, 52.95; H, 4.63; Cl, 13.02; N, 10.29; S, 5.89.

Found: C, 53.34; H, 4.74; Cl, 12.87; N, 9.92; S, 5.77.

[1054]

[Example 102]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

[1055]

^{1}H-NMR (DMSO-d_6) δ: 1.75-1.85(1H,br), 2.02-2.13(1H,br), 3.50-3.73(6H,m), 3.92-3.96(1H,br), 7.00(1H,m), 7.28-7.35(1H,m), 7.43-7.52(2H,m), 7.58(1H,d,J=7.8Hz), 7.74-7.78(1H,m), 7.93-8.07(2H,m), 8.14-8.36(2H,m), 8.83-8.95(2H,m), 12.43(1H,m).

MS (FAB) m/z: 495 [(M+H)$^+$, Cl^{35}], 497 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_4O_3S \cdot 1.05HCl \cdot 0.85H_2O$

Calculated: C, 54.73; H, 4.73; Cl, 13.25; N, 10.21; S, 5.85.

Found: C, 55.04; H, 5.03; Cl, 13.23; N, 9.89; S, 5.61.

[1056]

[Example 103]

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

[1057]

^{1}H-NMR ($CDCl_3$) δ: 2.85-3.40(4H,br), 3.06(1H,s), 3.40-4.10(4H,br), 7.01(1H,br s), 7.39(1H,d,J=8.8Hz), 7.45(2H,d,J=8.3Hz), 7.45-7.50(3H,m), 7.64(2H,d,J=8.3Hz), 7.89(1H,br s), 8.70(2H,d,J=6.8Hz), 9.55(1H,br s).

MS (FAB) m/z: 471 $(M+H)^+$

[1058]

[Example 104]

cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (50 ml), cis-4-[(1-benzensulfonyl-5-chloroindol-2-yl)sulfonyl]-1-(4-bromobenzoyl)-2,6-dimethylpiperazine (800 mg), diethyl 4-pyridylborane (255 mg), tetrabutylammonium bromide (275 mg) and tetrakis(triphenylphosphine) palladium (0) (175 mg) were dissolved, followed by the addition of potassium hydroxide (289 mg) and water (0.745 ml). The resulting mixture was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the residue and the organic layer was collected. The resulting

organic layer was washed with saturated saline, dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (2% methanol - dichloromethane), followed by crystallization from ethanol, whereby the title compound (580 mg, 53%) was obtained as colorless amorphous.

[1059]

^{1}H-NMR (DMSO-d_6) δ: 1.33(6H,br), 2.60-2.70(2H,m), 3.40-3.60(2H,m), 3.70-4.10(1H,br), 4.40-4.90(1H,br), 7.02(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.72(2H,d,J=5.4Hz), 7.75-7.85(3H,m), 8.65(2H,d,J=5.4Hz), 12.43(1H,s).

Elementary analysis for $C_{26}H_{25}ClN_4O_3S \cdot 0.3H_2O$

Calculated: C, 60.70; H, 5.02; Cl, 6.89; N, 10.89; S, 6.23.

Found: C, 61.03; H, 5.06; Cl, 7.09; N, 10.51; S, 6.09.

[1060]

[Example 105]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In a mixed solvent of dimethoxyethane (10 ml) and methanol (10 ml), 1-[(5-bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (485 mg) and 4-pyridylboric acid (197 mg) were suspended at room temperature, followed by the successive addition of tetrakis(triphenylphosphine) palladium (0) (116 mg) and cesium fluoride (1.00 g). The resulting mixture was heated under

reflux for 1 week. After the reaction mixture was cooled to room temperature, it was concentrated under reduced pressure. Dichloromethane and water were added to the concentrate and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (2% methanol - dichloromethane). The pale yellow crystals precipitated in ethanol were collected by filtration and dissolved in dichloromethane. To the resulting solution, 1N ethanol hydrochloride was added and the resulting mixture was distilled under reduced pressure to remove the solvent. The yellow crystals precipitated in ethyl acetate were collected by filtration and dried, whereby the title compound (40%) was obtained.

[1061]

^{1}H-NMR (DMSO-d_6) δ: 2.96(2H,br s), 3.16(2H,br s), 3.38(2H,br s), 3.81(2H,br s), 7.05(1H,d,J=2.0Hz), 7.35(1H,dd,J=8.8,2.0Hz), 7.51(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.13(2H,d,J=5.9Hz), 8.87(2H,d,J=5.9Hz), 9.37(2H,s), 12.48(1H,s).

MS (FAB) m/z: 483 [$(M+H)^+$, Cl^{35}], 485 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_3S \cdot 0.9HCl \cdot 1.4H_2O$

Calculated: C, 48.84; H, 4.23; Cl, 12.45; N, 15.53; S, 5.93.

Found: C, 49.11; H, 4.27; Cl, 12.26; N, 15.34; S, 5.91.

[1062]

In the same manner as in Example 6, the compounds shown in Examples 106 to 120 were synthesized.

[1063]

[Example 106]

4-[4-[[4-[(6-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1064]

^{1}H-NMR ($CDCl_3$) δ: 2.90-4.10(8H,br), 7.02(1H,d,J=1.0Hz), 7.22(1H,dd,J=8.8,1.7Hz), 7.46(2H,d,J=8.3Hz), 7.47(1H,s), 7.50(2H,d,J=7.3Hz), 7.60(2H,d,J=8.3Hz), 8.63(1H,d,J=8.8Hz), 8.29(2H,d,J=7.3Hz), 9.32(1H,br s).

Elementary analysis for $C_{24}H_{21}ClN_4O_4S \cdot 1.7H_2O$

Calculated: C, 54.64; H, 4.66; Cl, 6.72; N, 10.62; S, 6.08.

Found: C, 54.63; H, 4.65; Cl, 6.91; N, 10.42; S, 6.07.

[1065]

[Example 107]

4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1066]

^{1}H-NMR (DMSO-d_6) δ: 3.00-3.20(4H,br), 3.34-3.58(2H,br), 3.60-3.84(2H,br), 7.03(1H,s), 7.34(1H,d,J=8.8Hz), 7.47(2H,d,J=7.3Hz), 7.51(1H,d,J=8.8Hz), 7.79(2H,d,J=5.9Hz), 7.80(1H,s), 7.81(2H,d,J=7.3Hz), 8.28(2H,d,J=5.9Hz), 12.43(1H,br).

MS (FAB) m/z: 497 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}ClN_4O_4S \cdot 0.2H_2O$

Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.60; H, 4.38; Cl, 7.26; N, 11.09; S, 6.16.

[1067]

[Example 108] 4-[4-[[4-[(5-Chloro-1-methylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1068]

^{1}H-NMR ($CDCl_3$) δ: 3.06-3.45(4H,br), 3.48-4.06(4H,br), 4.00(3H,s), 7.07(1H,m), 7.33(1H,d,J=8.8Hz), 7.35(2H,dd,J=8.8,1.8Hz), 7.45-7.57(4H,m), 7.61(2H,d,J=8.3Hz), 7.66(1H,d,J=2.0Hz), 8.27(2H,d,J=6.8Hz).

MS (FAB) m/z: 511 [$(M+H)^+$, Cl^{35}], 513 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_4O_4S \cdot 0.9H_2O \cdot 0.05CH_2Cl_2$

Calculated: C, 56.61; H, 4.72; Cl, 7.34; N, 10.54; S, 6.03.

Found: C, 56.51; H, 4.71; Cl, 7.51; N, 10.37; S, 6.29.

[1069]

[Example 109]

2-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1070]

^{1}H-NMR (DMSO-d_6) δ: 3.04-3.18(4H,br), 3.37-3.83(4H,br), 7.03(1H,s), 7.33(1H,d,J=8.8Hz), 7.38-7.44(2H,m), 7.45(2H,d,J=7.3Hz), 7.50(1H,d,J=8.8Hz), 7.61-7.67(1H,m), 7.80(1H,s), 7.85(2H,d,J=7.3Hz), 8.33(1H,m), 12.40(1H,br).

MS (FAB) m/z: 497 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{21}ClN_4O_4S \cdot 0.2H_2O$

Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.72; H, 4.58; Cl, 7.13; N, 10.86; S, 6.29.

[1071]

[Example 110] 4-[4-[[4-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1072]

^{1}H-NMR (DMSO-d_6) δ: 1.30(3H,t,J=6.8Hz), 3.18-3.38(4H,br), 3.40-3.61(2H,br), 3.62-3.84(2H,br), 4.46(2H,q,J=6.8Hz), 7.16(1H,s), 7.41(1H,dd,J=8.8,2.0Hz), 7.52(2H,d,J=7.3Hz), 7.72(1H,d,J=8.8Hz), 7.78-7.88(5H,m), 8.28(2H,d,J=7.3Hz).

MS (FAB) m/z: 525 [$(M+H)^+$, Cl^{35}], 527 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{25}ClN_4O_4S \cdot 0.4H_2O$

Calculated: C, 58.67; H, 4.89; Cl, 6.66; N, 10.53; S, 6.02.

Found: C, 58.73; H, 4.91; Cl, 6.88; N, 10.26; S, 5.96.

[1073]

[Example 111]

4-[4-[[4-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1074]

^{1}H-NMR (DMSO-d_6) δ: 2.67(3H,s), 3.12-3.29(4H,br), 3.37-3.86(4H,br), 7.48(2H,d,J=8.3Hz), 7.65(1H,dd,J=8.8,2.0Hz), 7.80(2H,d,J=7.3Hz), 7.81(2H,d,J=8.3Hz), 8.12(1H,d,J=2.0Hz), 8.15(1H,d,J=8.8Hz), 8.27(2H,d,J=7.3Hz).

MS (FAB) m/z: 528 [$(M+H)^+$, Cl^{35}], 530 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{22}ClN_3O_4S_2 \cdot 0.7H_2O$

Calculated: C, 55.54; H, 4.36; Cl, 6.56; N, 7.77; S, 11.86.

Found: C, 55.73; H, 4.40; Cl, 6.67; N, 7.52; S, 11.72.

[1075]

[Example 112]

4-[4-[[cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1076]

^{1}H-NMR (DMSO-d_6) δ: 1.32(6H,br), 2.60-2.70(2H,m), 3.40-3.60(2H,m), 3.80-4.10(1H,br), 4.50-4.90(1H,br), 7.01(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.75-7.85(5H,m), 8.27(2H,d,J=6.8Hz), 12.44(1H,s).

Elementary analysis for $C_{26}H_{25}ClN_4O_4S \cdot 0.5H_2O$

Calculated: C, 58.48; H, 4.91; Cl, 6.64; N, 10.49; S, 6.00.

Found: C, 58.68; H, 5.02; Cl, 6.72; N, 10.51; S, 6.04.

[1077]

[Example 113]

4-[4-[[4-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1078]

^{1}H-NMR ($CDCl_3$) δ: 3.20-3.50(4H,br), 3.50-4.05(4H,br), 7.34(1H,s), 7.45-7.53(6H,m), 7.62(2H,d,J=7.8Hz), 7.69(1H,s).

MS (FAB) m/z: 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_5S \cdot 0.25H_2O$

Calculated: C, 57.37; H, 4.11; Cl, 7.06; N, 8.36; S, 6.38.

Found: C, 57.31; H, 4.30; Cl, 7.17; N, 8.22; S, 6.40.

[1079]

[Example 114]

4-[4-[[4-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1080]

^{1}H-NMR ($CDCl_3$) δ: 3.20-3.50(4H,br), 3.50-4.10(4H,br), 3.65-3.85(2H,br), 7.35-7.41(2H,br), 7.46-7.55(5H,br), 7.58-7.67(5H,m), 8.27(2H,d,J=5.9Hz).

HRMS (FAB) m/z: 498.0901 $(M+H)^+$ (calcd for $C_{24}H_{21}ClN_3O_5S$ 498.0890).

[1081]

[Example 115]

4-[4-[[4-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1082]

^{1}H-NMR (DMSO-d_6) δ: 3.02-3.90(8H,m), 7.59(2H,d,J=8.3Hz), 7.64(1H,d,J=2.0Hz), 8.01-8.05(3H,m), 8.18(1H,d,J=2.0Hz), 8.20(1H,d,J=8.8Hz), 8.31(2H,d,J=6.3Hz), 8.94(2H,d,J=6.3Hz).

MS (FAB) m/z: 514 [$(M+H)^+$, Cl^{35}], 516 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_3S_2 \cdot 0.8H_2O$

Calculated: C, 54.55; H, 4.12; Cl, 6.71; N, 7.95; S, 12.14.

Found: C, 54.66; H, 4.09; Cl, 6.95; N, 7.77; S, 11.87.

[1083]

[Example 116]

4-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1084]

^{1}H-NMR (DMSO-d_6) δ: 3.16-3.88(8H,m), 7.48(2H,d,J=8.3Hz), 7.58(1H,dd,J=8.8,2.0Hz), 7.77(1H,d,J=7.3Hz), 7.79(1H,s), 7.81(2H,d,J=8.8Hz), 8.08(2H,d,J=8.8Hz), 8.27(1H,d,J=7.3Hz), 8.33(1H,s).

MS (FAB) m/z: 514 [(M+H)$^+$, Cl^{35}], 516 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S_2 \cdot 1.2H_2O$

Calculated: C, 53.82; H, 4.22; Cl, 6.62; N, 7.84; S, 11.97.

Found: C, 53.66; H, 4.22; Cl, 6.81; N, 7.61; S, 11.72.

[1085]

[Example 117]

2-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1086]

^{1}H-NMR (DMSO-d_6) δ: 3.06-3.94(8H,m), 7.38-7.42(2H,m), 7.46(2H,d,J=8.3Hz), 7.54-7.63(2H,m), 7.86(2H,d,J=8.3Hz), 8.07(2H,t,J=4.4Hz), 8.27-8.34(2H,m).

MS (FAB) m/z: 514 [(M+H)$^+$, Cl^{35}], 516 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_3O_4S_2 \cdot 0.5H_2O \cdot 0.1CH_2Cl_2$

Calculated: C, 54.56; H, 4.01; Cl, 7.99; N, 7.89; S, 12.04.

Found: C, 54.93; H, 3.95; Cl, 7.90; N, 7.74; S, 11.71.

[1087]

[Example 118]

4-[4-[[4-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1088]

^{1}H-NMR ($CDCl_3$) δ: 3.40-4.00(8H,m), 7.50(2H,d,J=7.3Hz), 7.51(2H,d,J=8.3Hz), 7.58(1H,dd,J=8.8,2.0Hz), 7.63(2H,d,J=8.3Hz), 7.93(1H,d,J=8.8Hz), 8.19(1H,d,J=2.0Hz), 8.27(2H,d,J=7.3Hz).

MS (FAB) m/z: 515 [$(M+H)^+$, Cl^{35}], 517 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{19}ClN_4O_4S_2 \cdot 0.1H_2O$

Calculated: C, 53.45; H, 3.74; Cl, 6.86; N, 10.84; S, 12.41.

Found: C, 53.19; H, 3.72; Cl, 7.09; N, 10.70; S, 12.29.

[1089]

[Example 119]

4-[4-[[4-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1090]

^{1}H-NMR (DMSO-d_6) δ: 3.30-3.85(8H,m), 7.50(2H,d,J=8.3Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.80(2H,d,J=7.3Hz), 7.83(2H,d,J=8.3Hz), 8.28(2H,d,J=7.3Hz), 8.29(1H,d,J=8.8Hz), 8.50(1H,d,J=2.0Hz).

MS (FAB) m/z: 515 [$(M+H)^+$, Cl^{35}], 517 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{19}ClN_4O_4S_2$

Calculated: C, 53.64; H, 3.72; Cl, 6.88; N, 10.88; S, 12.45.

Found: C, 53.64; H, 3.99; Cl, 6.63; N, 10.90; S, 12.30.

[1091]

[Example 120]

4-[4-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

[1092]

^{1}H-NMR ($CDCl_3$) δ: 2.80-3.90(8H,br), 4.05(1H,s), 7.06(1H,br s), 7.39(1H,d,J=8.8Hz), 7.43-7.52(3H,m), 7.77-7.86(4H,m), 7.89(1H,br s), 8.27(2H,d,J=6.8Hz), 12.43(1H,br s).

MS (FAB) m/z: 487 $(M+H)^+$.

Elementary analysis for $C_{26}H_{22}N_4O_4S \cdot H_2O$

Calculated: C, 61.89; H, 4.79; N, 11.10; S, 6.36.

Found: C, 62.00; H, 4.67; N, 11.08; S, 6.35.

[1093]

[Example 121]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example 4, a reaction was effected, whereby the title compound was obtained.

[1094]

^{1}H-NMR (DMSO-d_6) δ: 3.06(2H,br), 3.14(2H,br), 3.45-3.85(4H,m), 7.74(1H,d,J=8.3Hz), 7.83(1H,d,J=8.8Hz), 8.19(1H,d,J=8.3Hz), 8.25-8.29(2H,m), 8.31(2H,d,J=5.9Hz), 8.52(1H,br s), 8.89(2H,d,J=5.9Hz), 9.02(2H,s).

MS (FAB) m/z: 494 [$(M+H)^+$, Cl^{35}], 496 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_3S \cdot HCl \cdot H_2O$

Calculated: C, 52.56; H, 4.23; Cl, 12.93; N, 12.77; S, 5.85.

Found: C, 52.47; H, 4.20; Cl, 13.09; N, 12.60; S, 5.98.

[1095]

[Example 122]

4-[5-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

In the same manner as in Example 6, a reaction was effected, whereby the title compound was obtained.

[1096]

^{1}H-NMR ($CDCl_3$) δ: 3.05-3.30(4H,br), 3.55-4.00(4H,br), 7.61(1H,dd,J=8.3 and 2.0Hz), 7.76(1H,dd,J=8.8 and 2.0Hz), 7.91-7.97(3H,m), 8.25-8.29(2H,m), 8.31-8.35(3H,m), 8.77(2H,s).

MS (FAB) m/z: 510 [$(M+H)^+$, Cl^{35}], 512 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_4S\cdot 0.8H_2O$

Calculated: C, 54.97; H, 4.15; Cl, 6.76; N, 13.36; S, 6.11.

Found: C, 54.99; H, 4.08; Cl, 6.75; N, 13.24; S, 6.20.

[1097]

[Example 123]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example 105, the title compound was obtained.

[1098]

^{1}H-NMR (DMSO-d_6) δ: 2.94(2H,br s), 3.13(2H,br s), 3.37(2H,br s), 3.80(2H,br s), 7.74(1H,dd,J=8.8,2.4Hz),

7.83(1H,dd,J=8.8,2.0Hz), 8.05-8.18(2H,br), 8.19(1H,d,J=8.8Hz), 8.25-8.32(2H,m), 8.52(1H,br s), 8.82-8.91(2H,br), 9.33-9.38(2H,m).

MS (FAB) m/z: 494 [$(M+H)^+$, Cl^{35}], 496 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_3S \cdot 0.95HCl \cdot 0.5H_2O$

Calculated: C, 53.62; H, 4.12; Cl, 12.86; N, 13.03; S, 5.96.

Found: C, 53.50; H, 4.09; Cl, 12.76; N, 12.87; S, 5.91.

[1099]

[Example 124]

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1100]

^{1}H-NMR ($CDCl_3$) δ: 3.14-3.17(2H,m), 3.25-3.28(2H,m), 3.55-3.58(2H,m), 3.94-3.98(2H,m), 7.50(2H,d,J=7.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.91-7.96(3H,m), 8.30-8.35(3H,m), 8.98(2H,s).

MS (FAB) m/z: 510 [$(M+H)^+$, Cl^{35}], 512 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_4S \cdot 0.6H_2O$

Calculated: C, 55.35; H, 4.10; Cl, 6.81; N, 13.45; S, 6.16.

Found: C, 55.01; H, 4.01; Cl, 7.00; N, 13.28; S, 6.28.

[1101]

[Example 125]

4-[4-[[4-[(6-Bromonaphthalen-2-yl)sulfonyl]piperazin-1-

yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 1, the title compound was obtained using 4-[4-[(piperazin-1-yl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (6-bromonaphthalen-2-yl)sulfonyl chloride as raw materials.

[1102]

^{1}H-NMR ($CDCl_3$) δ: 2.80-3.40(4H,br), 3.40-4.05(4H,br), 7.43(2H,d,J=7.8Hz), 7.47(2H,d,J=7.1Hz), 7.58(2H,d,J=7.8Hz), 7.70-7.78(2H,m), 7.85(1H,d,J=8.8Hz), 7.92(1H,d,J=8.8Hz), 8.13(1H,s), 8.26(2H,d,J=7.1Hz), 8.30(1H,s).

MS (FAB) m/z: 552 [$(M+H)^+$, Br^{79}], 554 [$(M+H)^+$, Br^{81}].

Elementary analysis for $C_{26}H_{22}BrN_3O_4S \cdot 0.5H_2O$

Calculated: C, 55.62; H, 4.13; N, 7.48; Br, 14.23; S, 5.71.

Found: C, 55.36; H, 3.89; N, 7.41; Br, 14.20; S, 5.59.

[1103]

[Example 126]

1-[(6-Bromonaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 1, a reaction was effected, whereby the title compound was obtained.

[1104]

^{1}H-NMR ($CDCl_3$) δ: 2.80-3.40(4H,br), 3.40-4.10(4H,br), 7.43(2H,d,J=8.3Hz), 7.47(2H,d,J=5.6Hz), 7.63(2H,d,J=8.3Hz), 7.72-7.78(2H,m), 7.86(1H,d,J=8.8Hz), 7.92(1H,d,J=8.8Hz), 8.13(1H,d,J=1.5Hz), 8.30(1H,s), 8.68(2H,d,J=5.6Hz).

MS (FAB) m/z: 536 [$(M+H)^+$, Br^{79}], 538 [$(M+H)^+$, Br^{81}].

Elementary analysis for $C_{26}H_{22}BrN_3O_3S \cdot 0.5H_2O$

Calculated: C, 57.25; H, 4.25; N, 7.70; Br, 14.65; S, 5.88.

Found: C, 57.51; H, 3.96; N, 7.67; Br, 14.76; S, 6.01.

[1105]

[Example 127]

1-[(6-Ethynylnaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

To a solution of 1-[(6-bromonaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (310 mg) and triphenylphosphine (455 mg) in tetrahydrofuran (tetrahydrofuran: 1.0 ml), triethylamine (3.0 ml), N,N-dimethylformamide (1.0 ml), trimethylsilylacetylene (130 ml) and palladium acetate (13.0 mg) were added, followed by heating under reflux for 2 hours. After the reaction mixture was allowed to cool down to room temperature, dichloromethane (15 ml) and water (30 ml) were added and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane : acetone = 3:1), whereby colorless amorphous was obtained. The resulting product was dissolved in methanol (25 ml), followed by the addition of tetrahydrofuran (5.0 ml) and potassium carbonate (300 mg). The resulting mixture was stirred for 30 minutes. Dichloromethane (30 ml) and water (50 ml) were added

to the reaction mixture and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane : acetone = 4:1), followed by pulverization and washing in a mixed solvent of dichloromethane, acetone and water, whereby the title compound (210 mg, 75%) was obtained.

[1106]

^{1}H-NMR ($CDCl_3$) δ: 2.80-4.10(8H,br), 7.43(2H,d,J=8.3Hz), 7.47(2H,d,J=6.4Hz), 7.67(2H,d,J=8.3Hz), 7.68(1H,dd,J=8.8,1.5Hz), 7.75(1H,dd,J=8.3,1.5Hz), 7.93(1H,d,J=8.3Hz), 7.97(1H,d,J=8.8Hz), 8.11(1H,s), 8.30(1H,s), 8.68(2H,d,J=6.4Hz).

MS (FAB) m/z: 482 $(M+H)^+$.

Elementary analysis for $C_{28}H_{23}N_3O_3S \cdot 0.4H_2O$

Calculated: C, 68.81; H, 4.91; N, 8.60; S, 6.56.

Found: C, 68.96; H, 4.91; N, 8.47; S, 6.52.

[1107]

[Example 128]

4-[4-[[4-[(6-Ethynylnaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example, the title compound was obtained.

[1108]

^{1}H-NMR ($CDCl_3$) δ: 2.95-4.00(8H,br), 7.42(2H,d,J=8.3Hz), 7.46(2H,d,J=6.8Hz), 7.58(2H,d,J=8.3Hz), 7.68(1H,dd,J=8.8,1.5Hz), 7.75(1H,dd,J=8.3,1.5Hz), 7.92(1H,d,J=8.8Hz), 7.95(1H,d,J=8.3Hz), 8.10(1H,s), 8.25(2H,d,J=6.8Hz), 8.30(1H,s).

MS (FAB) m/z: 498 [$(M+H)^+$].

Elementary analysis for $C_{28}H_{23}N_3O_4S \cdot H_2O$

Calculated: C, 65.23; H, 4.89; N, 8.15; S, 6.22.

Found: C, 65.41 H, 5.14; N, 8.19; S, 6.11.

[1109]

[Example 129]

4-[(1-Benzensulfonyl-5-chloroindol-2-yl)sulfonyl]-2-carbamoylmethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 7 or Example 1, a reaction was effected, whereby the title compound was obtained.

[1110]

^{1}H-NMR ($CDCl_3$) δ: 2.44-3.28(4H,m), 3.50-4.14(2H,m), 4.45-4.78(1H,m), 5.58-5.79(1H,m), 7.44-7.65(13H,m), 7.69(2H,d,J=8.3Hz), 8.05(2H,d,J=8.3Hz), 8.13-8.17(1H,m), 8.69(2H,d,J=5.9Hz).

MS (FAB) m/z: 678 [$(M+H)^+$, Cl^{35}], 680 [$(M+H)^+$, Cl^{37}].

[1111]

[Example 130]

2-Carbamoylmethyl-4-[(5-chloroindol-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 99, the title compound was obtained.

[1112]

^{1}H-NMR (DMSO-d_6) δ: 2.55-2.80(2H,m), 3.00-4.56(6H,m), 5.05-5.17(1H,m), 6.90-7.05(2H,m), 7.34(1H,dd,J=8.8,2.2Hz), 7.40-7.63(4H,m), 7.79(1H,m), 7.99(1H,m), 8.24(2H,br), 8.90(1H,m), 12.43(1H,s).

MS (FAB) m/z: 538 [$(M+H)^+$, Cl^{35}], 540 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{24}ClN_5O_4S \cdot 1.2HCl \cdot 2.5H_2O$

Calculated: C, 49.82; H, 4.86; Cl, 12.44; N, 11.17; S, 5.12.

Found: C, 50.14; H, 5.07; Cl, 12.54; N, 10.80; S, 5.18.

[1113]

[Example 131]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example 4, a reaction was effected, whereby the title compound was obtained.

[1114]

^{1}H-NMR (DMSO-d_6) δ: 3.08(2H,br), 3.18(2H,br), 3.52(2H,br), 3.77(2H,br), 7.04(1H,d,J=1.5Hz), 7.34(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.80(1H,d,J=2.0Hz), 8.48-8.53(2H,m), 8.91-8.95(2H,m), 9.07(2H,s), 12.46(1H,br s).

MS (FAB) m/z: 483 [$(M+H)^+$, Cl^{35}], 485 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_3S \cdot HCl \cdot 1.3H_2O \cdot 0.2EtOH$

Calculated: C, 48.74; H, 4.35; Cl, 12.84; N, 15.22; S, 5.81.

Found: C, 48.87; H, 4.38; Cl, 12.82; N, 15.02; S, 5.86.

[1115]

[Example 132]

1-[(6-Chlorobenzothiophen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example 105, the title compound was obtained.

[1116]

^{1}H-NMR (DMSO-d_6) δ: 3.03-3.06(2H,m), 3.20-3.23(2H,m), 3.41-3.44(2H,m), 3.83-3.86(2H,m), 7.61(1H,dd,J=8.8,2.0Hz), 8.10(1H,d,J=8.8Hz), 8.13(1H,s), 8.30-8.40(3H,m), 8.90-9.02(2H,br), 9.40-9.46(2H,m).

MS (FAB) m/z: 500 [$(M+H)^+$, Cl^{35}], 502 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{18}ClN_5O_3S \cdot HCl \cdot 0.7H_2O$

Calculated: C, 48.13; H, 3.74; Cl, 12.91; N, 12.75; S, 11.68.

Found: C, 47.95; H, 3.78; Cl, 13.13; N, 12.65; S, 11.53.

[1117]

[Example 133]

4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example 6, a reaction was effected, whereby the title compound was obtained.

[1118]

^{1}H-NMR ($CDCl_3$) δ: 3.24(2H,br), 3.34(2H,br), 3.60(2H,br), 3.98(2H,br), 7.47(1H,dd,J=8.8,2.0Hz), 7.52(2H,d,J=7.3Hz),

7.79(1H,s), 7.83(1H,d,J=8.8Hz), 7.88(1H,br s), 8.33(2H,d,J=7.3Hz), 9.00(2H,s).

MS (FAB) m/z: 516 [(M+H)$^+$, Cl^{35}], 518 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{18}ClN_5O_4S \cdot 0.4H_2O$

Calculated: C, 50.50; H, 3.62; Cl, 6.78; N, 13.39; S, 12.26.

Found: C, 50.24; H, 3.62; Cl, 7.14; N, 13.19; S, 12.04.

[1119]

[Example 134]

4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example 6, a reaction was effected, whereby the title compound was obtained.

[1120]

^{1}H-NMR (DMSO-d_6) δ: 2.95(2H,br), 3.15(2H,br), 3.37(2H,br), 3.79(2H,br), 7.05(1H,s), 7.34(1H,dd,J=8.8,1.5Hz), 7.51(1H,d,J=8.8Hz), 7.80(1H,d,J=1.5Hz), 7.95(2H,d,J=7.3Hz), 8.37(2H,d,J=7.3Hz), 9.28(2H,s), 12.47(1H,s).

MS (FAB) m/z: 499 [(M+H)$^+$, Cl^{35}], 501 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_4S \cdot 0.5H_2O \cdot 0.2EtOH$

Calculated: C, 52.02; H, 4.13; Cl, 6.86; N, 16.25; S, 6.20.

Found: C, 52.03; H, 3.99; Cl, 7.18; N, 15.99; S, 6.16.

[1121]

[Example 135]

4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

In the same manner as in Example 6, a reaction was effected, whereby the title compound was obtained.

[1122]

^{1}H-NMR (DMSO-d_6) δ: 3.09(2H,br), 3.16(2H,br), 3.53(2H,br), 3.75(2H,br), 7.03(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.27(2H,d,J=7.3Hz), 8.34(2H,d,J=7.3Hz), 8.95(2H,s), 12.42(1H,br s).

MS (FAB) m/z: 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_4S \cdot H_2O$

Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 51.29; H, 4.34; Cl, 6.80; N, 15.90; S, 6.08.

[1123]

[Example 136]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example 105, the title compound was obtained.

[1124]

^{1}H-NMR (DMSO-d_6) δ: 3.20(2H,t,J=4.9Hz), 3.62-3.78(2H,m), 3.45-3.60(2H,m), 3.78(2H,t,J=4.9Hz), 4.63(2H,s), 4.64(2H,s), 7.35(1H,d,J=8.3Hz), 7.38(1H,d,J=8.3Hz), 7.42(1H,s), 8.22(2H,d,J=5.4Hz), 8.92(2H,d,J=5.4Hz), 9.44(2H,s).

MS (FAB) m/z: 485 [$(M+H)^+$, Cl^{35}], 487 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{21}ClN_6O_3S \cdot HCl \cdot 1.8H_2O$

Calculated: C, 47.71; H, 4.66; Cl, 12.80; N, 15.17; S, 5.79.

Found: C, 48.01; H, 4.39; Cl, 13.19; N, 14.74; S, 5.73.

[1125]

In the same manner as in Example 4, the compounds shown in Examples 137 and 138 were synthesized.

[1126]

[Example 137]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

[1127]

^{1}H-NMR (DMSO-d_6) δ: 3.01(2H,br), 3.14(2H,br), 3.62(2H,br), 3.81(2H,br), 7.74(1H,dd,J=8.8,2.0Hz), 7.84(1H,dd,J=8.8,2.0Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.31(2H,m), 8.46(2H,d,J=5.4Hz), 8.52(1H,br s), 8.91(3H,m), 9.47(1H,s).

MS (FAB) m/z: 494 [$(M+H)^+$, Cl^{35}], 496 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_3S \cdot HCl \cdot H_2O \cdot 0.2AcOEt$

Calculated: C, 52.62; H, 4.38; Cl, 12.53; N, 12.37; S, 5.66.

Found: C, 52.47; H, 4.51; Cl, 12.87; N, 12.09; S, 5.68.

[1128]

[Example 138]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

[1129]

^{1}H-NMR (DMSO-d_6) δ: 3.04(2H,br), 3.18(2H,br), 3.63(2H,br), 3.81(2H,br), 7.05(1H,s), 7.33(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.11(2H,d,J=6.4Hz),

8.77(2H,d,J=6.4Hz), 8.93(1H,d,J=1.5Hz), 9.34(1H,d,J=1.5Hz), 12.43(1H,br s).

MS (FAB) m/z: 483 [(M+H)$^+$, Cl^{35}], 485 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_3S \cdot H_2O$

Calculated: C, 52.75; H, 4.23; Cl, 7.08; N, 16.78; S, 6.40.

Found: C, 52.78; H, 4.27; Cl, 7.17; N, 16.67; S, 6.37.

[1130]

In the same manner as in Example 6, reaction was effected, whereby the compounds shown in Examples 139 and 140 were synthesized.

[1131]

[Example 139]

4-[5-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine N-oxide

[1132]

^{1}H-NMR ($CDCl_3$) δ: 3.19(2H,br), 3.26(2H,br), 3.88(2H,br), 3.94(2H,br), 7.59(1H,dd,J=8.8,2.0Hz), 7.78(1H,dd,J=8.8,2.0Hz), 7.91-7.95(3H,m), 7.98(2H,d,J=7.3Hz), 8.30(2H,d,J=7.3Hz), 8.32(1H,d,J=2.0Hz), 8.90(1H,d,J=1.5Hz), 8.99(1H,d,J=1.5Hz).

MS (FAB) m/z: 510 [(M+H)$^+$, Cl^{35}], 512 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{24}H_{20}ClN_5O_4S \cdot 1.1H_2O$

Calculated: C, 54.41; H, 4.22; Cl, 6.69; N, 13.22; S, 6.05.

Found: C, 54.27; H, 4.61; Cl, 6.99; N, 13.28; S, 6.12.

[1133]

[Example 140]

4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine N-oxide

[1134]

^{1}H-NMR (DMSO-d_6) δ: 3.03(2H,br), 3.17(2H,br), 3.63(2H,br), 3.80(2H,br), 7.04(1H,s), 7.33(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.80(1H,d,J=2.0Hz), 8.19(2H,d,J=7.3Hz), 8.37(2H,d,J=7.3Hz), 8.87(1H,d,J=1.5Hz), 9.31(1H,d,J=1.5Hz), 12.45(1H,br s).

MS (FAB) m/z: 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{22}H_{19}ClN_6O_4S \cdot H_2O$

Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 50.92; H, 4.05; Cl, 6.96; N, 15.88; S, 6.10.

[1135]

[Example 141]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(3-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example 4, a reaction was effected, whereby the title compound was obtained.

[1136]

^{1}H-NMR (DMSO-d_6) δ: 2.36(3H,s), 2.95-3.30(4H,br), 3.35-3.90(4H,br), 7.50(2H,d,J=8.8Hz), 7.53(2H,d,J=8.8Hz), 7.71(1H,d,J=5.4Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.24-8.30(2H,m), 8.50(1H,br s), 8.72(1H,d,J=5.4Hz), 8.80(1H,s).

MS (FAB) m/z: 506 [(M+H)$^+$, Cl^{35}], 508 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_3S \cdot 0.8HCl \cdot 1.5H_2O$

Calculated: C, 57.68; H, 4.98; Cl, 11.35; N, 7.48; S, 5.70.

Found: C, 57.50; H, 5.06; Cl, 11.35; N, 7.28; S, 5.95.

[1137]

[Example 142]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-3-methylpyridine N-oxide

In the same manner as in Example 6, a reaction was effected, whereby the title compound was obtained.

[1138]

^{1}H-NMR (CDCl$_3$) δ: 2.21(3H,s), 3.14(4H,br), 3.68(2H,br), 3.85(2H,br), 7.09(1H,d,J=6.8Hz), 7.32(2H,d,J=8.3Hz), 7.41(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.90-7.96(3H,m), 8.11(1H,dd,J=6.4,1.5Hz), 8.15(1H,br s), 8.31(1H,br s).

MS (FAB) m/z: 522 [(M+H)$^+$, Cl^{35}], 524 [(M+H)$^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot 0.1H_2O$

Calculated: C, 61.92; H, 4.66; Cl, 6.77; N, 8.02; S, 6.12.

Found: C, 61.76; H, 4.72; Cl, 7.04; N, 7.76; S, 6.30.

[1139]

[Example 143]

1-(4-Amidinobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example 4, a reaction was effected,

whereby the title compound was obtained.

[1140]

^{1}H-NMR (DMSO-d_6) δ: 3.03(2H,br s), 3.13(2H,br s), 3.30(2H,br s), 3.73(2H,br s), 7.56(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.78-7.85(3H,m), 8.18(1H,d,J=8.3Hz), 8.25-8.30(2H,m), 8.50(1H,s), 9.10(2H,br s), 9.38(2H,br s).

MS (FAB) m/z: 457 [$(M+H)^+$, Cl^{35}], 459 [$(M+H)^+$, Cl^{37}].

[1141]

[Example 144]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(4,5-dihydroimidazol-2-yl)benzoyl]piperazine

[1142]

^{1}H-NMR (DMSO-d_6) δ: 3.04(2H,br s), 3.13(2H,br s), 3.37(2H,br s), 3.74(2H,br s), 4.00(4H,s), 7.60(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8Hz), 8.11(2H,d,J=8.3Hz), 8.19(1H,d,J=8.8Hz), 8.26(1H,d,J=2.0Hz), 8.28(1H,d,J=8.8Hz), 8.50(1H,s), 11.00(2H,br s).

MS (FAB) m/z: 483 [$(M+H)^+$, Cl^{35}], 485 [$(M+H)^+$, Cl^{37}].

[1143]

[Example 145]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[2-(N-tert-butoxycarbonylamino)pyridin-4-yl]benzoyl]piperazine

In the same manner as in Example 4, the title compound was obtained.

[1144]

^{1}H-NMR ($CDCl_3$) δ: 1.54(9H,s), 3.00-3.30(4H,m), 3.40-4.10(4H,m), 7.14(1H,dd,J=5.4,1.5Hz), 7.38(2H,d,J=8.3Hz), 7.53(1H,br s), 7.60(1H,dd,J=8.8,2.0Hz), 7.67(2H,d,J=8.3Hz), 7.77(1H,dd,J=8.3,1.5Hz), 7.91-7.98(3H,m), 8.18(1H,d,J=1.5Hz), 8.29(1H,d,J=5.4Hz), 8.32(1H,s).

[1145]

[Example 146]

1-[4-(2-Aminopyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example 7, the title compound was obtained.

[1146]

^{1}H-NMR (DMSO-d_6) δ: 2.95-3.25(4H,m), 3.30-3.93(4H,m), 7.14-7.23(2H,m), 7.51(2H,d,J=8.3Hz), 7.66-7.75(1H,m), 7.76(2H,d,J=8.8Hz), 7.82(1H,m), 8.03(1H,d,J=6.8Hz), 8.05-8.12(2H,m), 8.13-8.30(3H,m), 8.50(1H,s), 13.60(1H,br).

MS (FAB) m/z: 507 [$(M+H)^+$, Cl^{35}], 509 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{23}ClN_4O_3SHCl \cdot 3.6H_2O$

Calculated: C, 51.34; H, 5.17; Cl, 11.66; N, 9.21; S, 5.27.

Found: C, 51.07; H, 5.24; Cl, 11.85; N, 9.10; S, 5.75.

[1147]

[Example 147]

2-tert-Butoxycarbonylamino-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was

obtained.

[1148]

^{1}H-NMR ($CDCl_3$) δ: 1.55(9H,s), 2.95-3.35(4H,br), 3.50-4.00(4H,m), 7.11(1H,dd,J=6.8,2.5Hz), 7.40(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.64(2H,d,J=8.3Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.91-7.98(3H,m), 8.25(1H,d,J=6.8Hz), 8.31(1H,d,J=2.0Hz), 8.42(1H,d,J=2.5Hz), 9.28(1H,s).

MS (FAB) m/z: 623 [$(M+H)^+$, Cl^{35}], 625 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{31}H_{31}ClN_4O_6S \cdot 0.1H_2O$

Calculated: C, 59.58; H, 5.03; Cl, 5.67; N, 8.97; S, 5.13.

Found: C, 59.43; H, 5.04; Cl, 5.95; N, 8.89; S, 5.17.

[1149]

[Example 148]

2-Amino-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 7, the title compound was obtained.

[1150]

^{1}H-NMR (DMSO-d_6) δ: 2.95-3.25(4H,br), 3.30-3.90(4H,m), 7.14(1H,dd,J=6.8,2.0Hz), 7.28(1H,d,J=2.0Hz), 7.49(2H,d,J=8.3Hz), 7.70-7.78(3H,m), 7.82(1H,dd,J=8.8,2.0Hz), 8.16(2H,br), 8.18(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.32(1H,d,J=6.8Hz), 8.50(1H,br s).

MS (FAB) m/z: 523 [$(M+H)^+$, Cl^{35}], 525 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{26}H_{23}ClN_4O_4S \cdot HCl \cdot 1.5H_2O$

Calculated: C, 53.25; H, 4.64; Cl, 12.09; N, 9.55; S, 5.47.

Found: C, 53.21; H, 4.67; Cl, 11.96; N, 9.53; S, 5.61.

[1151]

[Example 149]

4-[5-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyridin-2-yl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1152]

^{1}H-NMR ($CDCl_3$) δ: 3.00-3.40(4H,br s), 3.50-4.05(4H,m), 7.61(1H,dd,J=8.8,2.0Hz), 7.73-7.83(3H,m), 7.90-7.97(5H,m), 8.27(2H,d,J=7.3Hz), 8.31(1H,br s), 8.63(1H,m).

MS (FAB) m/z: 509 [$(M+H)^+$, Cl^{35}], 511 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{21}ClN_4O_4S \cdot 0.5H_2O$

Calculated: C, 57.97; H, 4.28; Cl, 6.84; N, 10.82; S, 6.19.

Found: C, 57.99; H, 4.51; Cl, 6.99; N, 10.54; S, 6.53.

[1153]

[Example 150]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[1-oxo-6-(1-oxopyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

In the same manner as in Example 6, the title compound was obtained.

[1154]

^{1}H-NMR ($CDCl_3$) δ: 3.15(4H,br s), 3.50-4.00(4H,m), 7.20-7.30(1H,m), 7.52(1H,d,J=8.3Hz), 7.61(1H,dd,J=8.8,2.0Hz),

7.76(1H,dd,J=8.8,2.0Hz), 7.89(2H,d,J=7.3Hz), 7.91-7.97(3H,m), 8.21(1H,d,J=1.5Hz), 8.26(2H,d,J=7.3Hz), 8.31(1H,br s).

MS (FAB) m/z: 525 [$(M+H)^+$, Cl^{35}], 527 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{21}ClN_4O_5S\cdot0.1H_2O$

Calculated: C, 57.00; H, 4.06; Cl, 6.73; N, 10.64; S, 6.09.

Found: C, 57.03; H, 4.23; Cl, 6.82; N, 10.34; S, 6.15.

[1155]

[Example 151]

1-[4-(2-Acetoxymethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In acetic anhydride (25 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide (900 mg) was dissolved, followed by heating under reflux for 15 minutes. Ethanol (25 ml) was added to the reaction mixture and the resulting mixture was heated under reflux for further 1 hour. To the reaction mixture, dichloromethane and an aqueous solution of sodium bicarbonate were added and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 1.5% methanol - dichloromethane), followed by crystallization from ethanol. The crystals were dissolved in dichloromethane and the resulting solution was made acidic by the addition of ethanolic hydrochloric acid. The resulting acidic mixture was

concentrated, whereby the title compound (842 mg, 87%, pale yellow powder) was obtained.

[1156]

^{1}H-NMR (DMSO-d_6) δ: 2.12(3H,s), 3.06(4H,br), 3.30-3.80(4H,br), 5.23(2H,s), 7.48(2H,d,J=8.3Hz), 7.72(1H,dd,J=8.8,2.4Hz), 7.78(1H,d,J=5.4Hz), 7.79-7.87(4H,m), 8.17(1H,d,J=8.8Hz), 8.23-8.29(2H,m), 8.49(1H,br s), 8.67(1H,d,J=5.4Hz).

MS (FAB) m/z: 564 [$(M+H)^+$, Cl^{35}], 566 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_5S \cdot 0.4HCl \cdot 0.7H_2O$

Calculated: C, 58.91; H, 4.74; Cl, 8.39; N, 7.11; S, 5.42.

Found: C, 58.86; H, 4.69; Cl, 8.29; N, 6.99; S, 5.41.

[1157]

[Example 152] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 3, the title compound was obtained.

[1158]

^{1}H-NMR (DMSO-d_6) δ: 3.08(4H,br), 3.47(2H,br), 3.71(2H,br), 4.66(2H,s), 7.49(2H,d,J=8.3Hz), 7.64(1H,d,J=5.4Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.78-7.85(4H,m), 8.18(1H,d,J=8.8Hz), 8.23-8.30(2H,m), 8.50(1H,br s), 8.58(1H,d,J=5.4Hz).

MS (FAB) m/z: 522 [$(M+H)^+$, Cl^{35}], 524 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_4S \cdot 0.25HCl \cdot 1.2H_2O$

Calculated: C, 58.67; H, 4.86; Cl, 8.02; N, 7.60; S, 5.80.

Found: C, 58.73; H, 4.77; Cl, 7.94; N, 7.39; S, 5.82.

[1159]

[Example 153]

2-Acetoxymethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1160]

^{1}H-NMR ($CDCl_3$) δ: 2.21(3H,s), 3.14(4H,br), 3.30-4.10(4H,br), 5.42(2H,s), 7.40-7.46(3H,m), 7.54-7.64(4H,m), 7.76(1H,d,J=7.3Hz), 7.90-7.97(3H,m), 8.29(1H,d,J=6.4Hz), 8.31(1H,br s).

MS (FAB) m/z: 580 [$(M+H)^+$, Cl^{35}], 582 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{26}ClN_3O_6S\cdot0.3H_2O$

Calculated: C, 59.49; H, 4.58; Cl, 6.06; N, 7.18; S, 5.48.

Found: C, 59.33; H, 4.63; Cl, 6.18; N, 7.26; S, 5.49.

[1161]

[Example 154]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-hydroxymethylpyridine N-oxide

In the same manner as in Example 3, the title compound was obtained.

[1162]

^{1}H-NMR ($CDCl_3$) δ: 3.06(4H,br), 3.30-3.90(4H,br), 4.63(2H,d,J=5.4Hz), 5.66(1H,t,J=5.4Hz), 7.46(2H,d,J=8.3Hz), 7.70(1H,dd,J=6.8,2.9Hz), 7.73(1H,dd,J=8.8,2.0Hz),

7.78(2H,d,J=8.3Hz), 7.80-7.84(2H,m), 8.18(1H,d,J=8.8Hz), 8.25-8.32(3H,m), 8.50(1H,br s).

MS (FAB) m/z: 538 [$(M+H)^+$, Cl^{35}], 540 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{24}ClN_3O_5S \cdot 0.4H_2O$

Calculated: C, 59.48; H, 4.58; Cl, 6.50; N, 7.71; S, 5.88.

Found: C, 59.60; H, 4.56; Cl, 6.50; N, 7.52; S, 5.92.

[1163]

[Example 155]

1-[4-(2-Aminomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

At room temperature, 1-[4-(2-azidomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (159 mg) was dissolved in tetrahydrofuran (5 ml), followed by the addition of water (0.5 ml) and triphenylphosphine (114 mg). The resulting mixture was stirred for 18 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (10% methanol - dichloromethane), followed by dissolution in dichloromethane. To the resulting solution, ethanolic 1N hydrochloric acid and water were added. The resulting mixture was then concentrated. The crystals were collected by filtration and washed with ethyl acetate, whereby the title compound (53 mg, 30%) was obtained.

[1164]

^{1}H-NMR (DMSO-d_6) δ: 3.07(4H,br), 3.30-4.20(4H,m), 4.24(1H,d,J=5.8Hz), 4.27(1H,d,J=5.8Hz), 7.51(2H,d,J=8.3Hz),

7.71-7.78(2H,m), 7.80-7.87(3H,m), 7.89(1H,br s), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.42(2H,br s), 8.50(1H,br s), 8.69(1H,d,J=5.4Hz).

MS (FAB) m/z: 521 [$(M+H)^+$, Cl^{35}], 523 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{25}ClN_4O_3S \cdot 1.5HCl \cdot 2.1H_2O$

Calculated: C, 52.85; H, 5.04; Cl, 14.45; N, 9.13; S, 5.23.

Found: C, 52.69; H, 4.93; Cl, 14.60; N, 9.21; S, 5.25.

[1165]

[Example 156]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[2-(dimethylaminomethyl)pyridin-4-yl]benzoyl]piperazine hydrochloride

In the same manner as in Referential Example 178, the corresponding brome compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine (300 mg) as a raw material. To the resulting compound, dimethylamine hydrochloride (469 mg) and potassium carbonate (795 mg) were added, followed by stirring for 24 hours. The solvent was then distilled off under reduced pressure. Ethyl acetate and water were added to the residue and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (3 to 5% methanol - dichloromethane). Ethanolic hydrochloric acid was added and the resulting mixture

was concentrated. Ethyl acetate was added to the concentrate. The colorless powder thus obtained was collected by filtration and dried, whereby the title compound (74 mg, 21%) was obtained.

[1166]

^{1}H-NMR (DMSO-d_6) δ: 2.82(6H,s), 3.07(4H,br), 3.30-3.90(4H,m), 4.50(2H,br s), 7.51(2H,d,J=7.8Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.79-7.85(2H,m), 7.86(2H,d,J=7.8Hz), 8.00(1H,br s), 8.19(1H,d,J=8.8Hz), 8.25-8.30(2H,m), 8.50(1H,br s), 8.73(1H,d,J=4.9Hz).

MS (FAB) m/z: 549 [$(M+H)^+$, Cl^{35}], 551 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{29}ClN_4O_3S \cdot 1.1HCl \cdot 2H_2O$

Calculated: C, 55.71; H, 5.50; Cl, 11.91; N, 8.96; S, 5.13.

Found: C, 55.61; H, 5.49; Cl, 11.89; N, 9.18; S, 5.27.

[1167]

[Example 157]

1-[4-[2-[(tert-Butoxycarbonylamino)methyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 10, a reaction was effected, whereby the title compound was obtained.

[1168]

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.13(4H,br), 3.40-4.00(4H,m), 4.50(2H,d,J=5.4Hz), 5.57(1H,br s), 7.35(1H,dd,J=5.4,1.5Hz), 7.41(2H,d,J=8.3Hz), 7.44(1H,br s), 7.57-7.65(3H,m), 7.76(1H,dd,J=8.3,1.5Hz), 7.90-7.97(3H,m), 8.31(1H,d,J=1.5Hz),

8.59(1H,d,J=5.4Hz).

MS (FAB) m/z: 621 [$(M+H)^+$, Cl^{35}], 623 [$(M+H)^+$, Cl^{37}].

[1169]

[Example 158]

2-[(tert-Butoxycarbonylamino)methyl]-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1170]

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 3.13(4H,br), 3.40-4.00(4H,m), 4.52(2H,d,J=6.3Hz), 5.86(1H,br s), 7.39-7.44(3H,m), 7.56-7.63(4H,m), 7.77(1H,dd,J=8.8,2.0Hz), 7.91-7.97(3H,m), 8.27(1H,d,J=6.8Hz), 8.31(1H,d,J=2.0Hz).

MS (FAB) m/z: 637 [$(M+H)^+$, Cl^{35}], 639 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{32}H_{33}ClN_4O_6S \cdot 0.7H_2O$

Calculated: C, 59.15; H, 5.34; Cl, 5.46; N, 8.62; S, 4.94.

Found: C, 58.92; H, 5.41; Cl, 5.56; N, 8.52; S, 5.05.

[1171]

[Example 159]

2-Aminomethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 7, the title compound was obtained.

[1172]

^{1}H-NMR (DMSO-d_6) δ: 3.07(4H,br), 3.35-3.95(4H,m), 4.24(2H,d,J=5.4Hz), 7.49(2H,d,J=8.3Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.80-7.87(3H,m), 7.89(1H,dd,J=6.8,2.4Hz), 8.17-8.22(2H,m), 8.25-8.30(2H,m), 8.45(1H,d,J=6.8Hz), 8.51(1H,br s), 8.71(3H,br s).

MS (FAB) m/z: 537 [$(M+H)^+$, Cl^{35}], 539 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{25}ClN_4O_4S \cdot 1.7HCl \cdot H_2O$

Calculated: C, 52.56; H, 4.69; Cl, 15.51; N, 9.08; S, 5.20.

Found: C, 52.69; H, 4.85; Cl, 15.51; N, 8.90; S, 5.13.

[1173]

[Example 160]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-cyanopyridin-4-yl)benzoyl]piperazine

In dichloromethane (100 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide (1.67 g) was dissolved, followed by the addition of trimethylsilylnitrile (0.42 ml) and dimethylcarbamoyl chloride (0.30 ml). The resulting mixture was stirred at room temperature for 24 hours. An aqueous solution of sodium bicarbonate and dichloromethane were added to the reaction mixture and the organic layer was collected. The resulting organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (1% methanol - dichloromethane), whereby the title compound (1.44 g, 84%) was obtained.

[1174]

^{1}H-NMR ($CDCl_3$) δ: 3.14(4H,br s), 3.49(2H,br s), 3.89(2H,br s), 7.47(2H,d,J=8.3Hz), 7.55-7.72(4H,m), 7.76(1H,dd,J=8.8,1.5Hz), 7.87(1H,s), 7.90-8.04(3H,m), 8.31(1H,br s), 8.77(1H,d,J=4.9Hz).

MS (FAB) m/z: 517 [$(M+H)^+$, Cl^{35}], 519 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{21}ClN_4O_3S \cdot 0.05CH_2Cl_2$

Calculated: C, 62.33; H, 4.08; Cl, 7.48; N, 10.75; S, 6.15.

Found: C, 62.16; H, 4.20; Cl, 7.65; N, 10.69; S, 6.04.

[1175]

[Example 161]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-cyanopyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1176]

^{1}H-NMR ($CDCl_3$) δ: 3.13(4H,br s), 3.60(2H,br s), 3.87(2H,br s), 7.46(2H,d,J=8.3Hz), 7.54-7.65(4H,m), 7.76(1H,dd,J=8.3,1.5Hz), 7.83(1H,d,J=2.9Hz), 7.90-7.97(3H,m), 8.28-8.33(2H,m).

MS (FAB) m/z: 533 [$(M+H)^+$, Cl^{35}], 535 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{27}H_{21}ClN_4O_4S$

Calculated: C, 60.84; H, 3.97; Cl, 6.65; N, 10.51; S, 6.02.

Found: C, 60.76; H, 4.04; Cl, 6.64; N, 10.39; S, 6.05.

[1177]

[Example 162]

1-[4-[2-[2-(tert-Butoxycarbonylamino)ethyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Example 3 or Example 4, a reaction was effected using methyl 4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoate as a raw material, whereby the title compound was obtained.

[1178]

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 3.04(2H,t,J=6.4Hz), 3.12(4H,br), 3.45-4.00(6H,m), 5.11(1H,br s), 7.31(1H,dd,J=5.4,2.0Hz), 7.35(1H,br s), 7.41(2H,d,J=8.3Hz), 7.58-7.65(3H,m), 7.77(1H,dd,J=8.3,1.5Hz), 7.90-7.97(3H,m), 8.31(1H,s), 8.59(1H,d,J=5.4Hz).

MS (FAB) m/z: 635 [$(M+H)^+$, Cl^{35}], 637 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{33}H_{35}ClN_4O_5S$

Calculated: C, 62.40; H, 5.55; N, 8.82.

Found: C, 62.78; H, 5.93; N, 8.51.

[1179]

[Example 162]

1-[4-[2-(2-Aminoethyl)pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example 7, the title compound was obtained.

[1180]

^{1}H-NMR (DMSO-d_6) δ: 3.08(4H,s), 3.23(2H,br), 3.30(2H,br), 3.45(2H,br), 3.73(2H,br), 7.52(2H,d,J=8.3Hz),

7.74(1H,dd,J=5.4,2.0Hz), 7.80-7.87(5H,m), 8.06(2H,br), 8.19(1H,d,J=8.8Hz), 8.25-8.31(2H,m), 8.51(1H,br s), 8.69(1H,d,J=4.4Hz).

MS (FAB) m/z: 535 [$(M+H)^+$, Cl^{35}], 537 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{27}ClN_4O_3S \cdot 1.85HCl \cdot 1.4H_2O$

Calculated: C, 53.57; H, 5.08; Cl, 16.10; N, 8.93; S, 5.11.

Found: C, 53.39; H, 5.06; Cl, 15.99; N, 8.81; S, 5.08.

[1181]

[Example 163]

4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1182]

^{1}H-NMR ($CDCl_3$) δ: 1.39(9H,s), 3.00-3.30(6H,m), 3.50-4.00(6H,m), 5.28(1H,br s), 7.37(1H,dd,J=6.8,2.9Hz), 7.41(2H,d,J=8.3Hz), 7.51(1H,br s), 7.56-7.63(3H,m), 7.77(1H,dd,J=8.3,1.5Hz), 7.91-7.97(3H,m), 8.28(1H,d,J=6.8Hz), 8.31(1H,d,J=1.5Hz).

MS (FAB) m/z: 651 [$(M+H)^+$, Cl^{35}], 653 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{33}H_{35}ClN_4O_6S \cdot 0.8H_2O$

Calculated: C, 59.55; H, 5.54; N, 8.42.

Found: C, 59.75; H, 5.61; N, 8.07.

[1183]

[Example 164]

2-(2-Aminoethyl)-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 7, the title compound was obtained using 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide as a raw material.

[1184]

^{1}H-NMR (DMSO-d_6) δ: 2.95-3.30(6H,m), 3.30-3.90(6H,m), 7.47(2H,d,J=8.3Hz), 7.71-8.10(8H,m), 8.19(1H,d,J=8.8Hz), 8.26-8.30(2H,m), 8.37(1H,d,J=6.8Hz), 8.51(1H,br s).

MS (FAB) m/z: 551 [$(M+H)^+$, Cl^{35}], 553 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{27}ClN_4O_4S \cdot 1.1HCl \cdot 1.6H_2O$

Calculated: C, 54.24; H, 5.09; Cl, 12.01; N, 9.04; S, 5.17.

Found: C, 54.40; H, 5.36; Cl, 11.90; N, 8.97; S, 5.27.

[1185]

[Example 165]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]-1,2,3,4-tetrahydropyrazine

In N,N-dimethylformamide (1 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (60 mg) and p-nitrophenyl 4-(pyridin-4-yl)benzoate (52 mg) were dissolved, followed by the addition of sodium hydride (60% in oil, 7.20 mg) under ice cooling. The resulting mixture was stirred for 1 hour. Water and ethyl acetate were added to the reaction mixture and the organic layer was collected. The resulting organic layer was dried over

anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 2:1), followed by dissolution in ethanol. To the resulting solution, ethanolic 1N hydrochloric acid was added and the resulting mixture was concentrated, whereby the title compound (58 mg, 60%) was obtained as pale yellow powder.

[1186]

^{1}H-NMR ($CDCl_3$) δ: 3.51(2H,s), 3.79(3H,s), 3.99(2H,s), 7.60(1H,dd,J=8.8,2.0Hz), 7.68(1H,br), 7.76(2H,d,J=7.8Hz), 7.90(2H,d,J=7.8Hz), 7.92-7.99(3H,m), 8.12(2H,d,J=5.4Hz), 8.16(1H,dd,J=8.8,1.5Hz), 8.58(1H,br s), 8.93(2H,d,J=5.4Hz).

MS (FAB) m/z: 548 [$(M+H)^+$, Cl^{35}], 550 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{22}ClN_3O_5S \cdot 0.8HCl \cdot 1.3H_2O$

Calculated: C, 55.99; H, 4.26; Cl, 10.63; N, 7.00; S, 5.34.

Found: C, 55.96; H, 4.31; Cl, 10.43; N, 6.94; S, 5.56.

[1187]

[Example 166]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl-1,2,3,4-tetrahydropyrazine

In the same manner as in Example 7, the title compound was obtained using 4-(4-bromobenzoyl)-1-[(6-chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1,2,3,4-tetrahydropyrazine as a raw material.

[1188]

^{1}H-NMR (DMSO-d_6) δ: 3.10-3.90(7H,m), 7.43(1H,s), 7.66(2H,d,J=8.3Hz), 7.78(1H,dd,J=8.8,2.0Hz), 7.96(1H,dd,J=8.8,2.0Hz), 8.02(2H,d,J=8.3Hz), 8.20-8.38(5H,m), 8.74(1H,br s), 8.94(2H,d,J=6.3Hz).

MS (FAB) m/z: 548 [$(M+H)^+$, Cl^{35}], 550 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{22}ClN_3O_5S \cdot 0.8HCl \cdot 0.5H_2O$

Calculated: C, 57.37; H, 4.09; Cl, 10.89; N, 7.17; S, 5.47.

Found: C, 57.24; H, 4.15; Cl, 10.88; N, 6.97; S, 5.29.

[1189]

[Example 167]

cis-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-cyanopyridin-4-yl)benzoyl]-2,6-dimethylpiperazine

In the same manner as in Example 160, the title compound was obtained.

[1190]

^{1}H-NMR ($CDCl_3$) δ: 1.40-1.60(6H,m), 2.40-2.60(2H,m), 3.40-3.90(3H,m), 4.40-4.90(1H,br), 7.43(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.64(2H,d,J=8.3Hz), 7.69(1H,dd,J=5.4,2.0Hz), 7.76(1H,dd,J=8.8,1.5Hz), 7.88(1H,d,J=2.0Hz), 7.90-7.95(3H,m), 8.31(1H,d,J=1.5Hz), 8.78(1H,d,J=5.4Hz).

MS (FAB) m/z: 545 [$(M+H)^+$, Cl^{35}], 547 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{25}ClN_4O_3S$

Calculated: C, 63.90; H, 4.62; Cl, 6.50; N, 10.28; S, 5.88.

Found: C, 63.87; H, 4.98; Cl, 6.33; N, 9.96; S, 5.75.

[1191]

[Example 168]

4-[4-[[cis-4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-yl]carbonyl]phenyl]-2-cyanopyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1192]

^{1}H-NMR ($CDCl_3$) δ: 1.42-1.55(6H,m), 2.43-2.60(2H,m), 3.40-3.90(3H,m), 4.40-4.90(1H,br), 7.42(2H,d,J=8.3Hz), 7.58(2H,d,J=8.3Hz), 7.60-7.65(2H,m), 7.76(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=2.9Hz), 7.90-7.95(3H,m), 8.29-8.32(2H,m).

MS (FAB) m/z: 561 [$(M+H)^+$, Cl^{35}], 563 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{29}H_{25}ClN_4O_4S\cdot0.3H_2O$

Calculated: C, 61.49; H, 4.56; Cl, 6.26; N, 9.89; S, 5.66.

Found: C, 61.47; H, 4.63; Cl, 6.13; N, 9.72; S, 5.73.

[1193]

[Example 169]

1-[4-[(3-Aminomethyl)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example 4 or Example 7, a reaction was effected, whereby the title compound was obtained.

[1194]

^{1}H-NMR (DMSO-d_6) δ: 3.07(4H,br), 3.51(2H,br), 3.69(2H,br), 4.09(2H,s), 7.45(2H,d,J=8.3Hz), 7.47-7.55(2H,m), 7.66-

7.76(4H,m), 7.80-7.87(2H,m), 8.19(2H,d,J=8.8Hz), 8.25-8.42(4H,m), 8.51(1H,br s).

MS (FAB) m/z: 520 [$(M+H)^+$, Cl^{35}], 522 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{28}H_{26}ClN_3O_3S \cdot HCl$

Calculated: C, 60.34; H, 4.89; Cl, 12.74; N, 7.55; S, 5.76.

Found: C, 60.15; H, 4.89; Cl, 12.44; N, 7.52; S, 5.80.

[1195]

[Example 170]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

In the same manner as in Example 4, the title compound was obtained.

[1196]

^{1}H-NMR (DMSO-d_6) δ: 2.94(2H,br s), 3.07(2H,br s), 3.52(2H,br s), 3.73(2H,br s), 7.74(1H,dd,J=8.8,2.4Hz), 7.84(1H,dd,J=8.8,2.0Hz), 7.99(2H,d,J=6.3Hz), 8.20(1H,d,J=8.8Hz), 8.26-8.31(2H,m), 8.53(1H,br s), 8.87(2H,d,J=6.3Hz).

MS (FAB) m/z: 511 [$(M+H)^+$, Cl^{35}], 513 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{23}H_{19}ClN_6O_4S \cdot 0.6HCl \cdot 1.5H_2O$

Calculated: C, 49.34; H, 4.07; Cl, 10.13; N, 15.01; S, 5.73.

Found: C, 49.25; H, 4.01; Cl, 10.12; N, 15.07; S, 5.59.

[1197]

[Example 171]

trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-

chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 105, the title compound was obtained as colorless amorphous powder by using trans-2,6-bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[1198]

^{1}H-NMR (DMSO-d_6) δ: 2.50-2.65(2H,m), 3.70-3.80(2H,m), 3.30-3.40(4H,m), 3.46(6H,s), 4.23(2H,br), 7.60(2H,d,J=8.3Hz), 7.74(1H,d,J=8.8Hz), 7.85(1H,d,J=8.3Hz), 8.03(2H,d,J=8.3Hz), 8.15-8.40(4H,m), 8.53(1H,s), 8.90-9.00(2H,m).

MS (FAB) m/z: 636 [$(M+H)^+$, Cl^{35}], 638 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{32}H_{30}ClN_3O_7S \cdot HCl \cdot 2.6H_2O$

Calculated: C, 53.42; H, 5.07; Cl, 9.86; N, 5.84; S, 4.46.

Found: C, 53.21; H, 4.75; Cl, 9.91; N, 5.80; S, 4.54.

[1199]

[Example 172]

cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 171, the title compound was obtained.

[1200]

^{1}H-NMR (DMSO-d_6) δ: 2.70-3.00(6H,m), 3.40-3.80(2H,m), 3.51(3H,s), 3.68(3H,s), 4.13(1H,br), 4.97(1H,br), 7.58(2H,d,J=7.8Hz), 7.70-7.75(1H,m), 7.80-7.90(1H,m),

8.03(2H,d,J=8.3Hz), 8.19(1H,d,J=8.8Hz), 8.25-8.35(4H,m), 8.55(1H,s), 8.90-8.95(2H,m).

MS (FAB) m/z: 636 [$(M+H)^+$, Cl^{35}], 638 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{32}H_{30}ClN_3O_7S \cdot HCl \cdot 0.3H_2O$

Calculated: C, 56.69; H, 4.70; Cl, 10.46; N, 6.20; S, 4.73.

Found: C, 56.72; H, 4.66; Cl, 10.31; N, 6.03; S, 4.71.

[1201]

[Example 173]

cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 35, the title compound was obtained using cis-2,6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine as a raw material.

[1202]

^{1}H-NMR (DMSO-d_6) δ: 2.30-2.60(10H,m), 2.80-2.90(2H,m), 3.45-3.55(1H,m), 3.75-3.85(1H,m), 4.10-4.20(1H,m), 4.95-5.05(1H,m), 6.85(1H,br s), 7.03(1H,br s), 7.40(1H,br s), 7.45(1H,br s), 7.56(2H,d,J=8.3Hz), 7.70-7.75(1H,m), 7.80-7.85(1H,m), 8.02(2H,d,J=8.3Hz), 8.18(1H,d,J=8.8Hz), 8.25-8.40(4H,m), 8.52(1H,s), 8.95(2H,d,J=6.8Hz).

MS (FAB) m/z: 606 [$(M+H)^+$, Cl^{35}], 608 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{30}H_{28}ClN_5O_5S \cdot 1.2HCl \cdot 2.8H_2O$

Calculated: C, 51.45; H, 5.01; N, 11.14; Cl, 10.00; S, 4.58.

Found: C, 51.52; H, 5.30; N, 11.33; Cl, 10.01; S, 4.72.

[1203]

[Example 174]

4-[4-[[cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1204]

^{1}H-NMR (DMSO-d_6) δ: 2.30-2.60(4H,m), 2.75-2.90(2H,m), 3.45-3.55(1H,m), 3.75-3.85(1H,m), 4.10-4.20(1H,m), 4.90-5.00(1H,m), 6.86(1H,br), 7.02(1H,br), 7.30-7.50(4H,m), 7.70-7.85(6H,m), 8.18(1H,d,J=8.8Hz), 8.25-8.35(4H,m), 8.52(1H,s).

MS (FAB) m/z: 622 [$(M+H)^+$, Cl^{35}], 624 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{30}H_{28}ClN_5O_6S \cdot 1.6H_2O$

Calculated: C, 55.36; H, 4.83; Cl, 5.45; N, 10.76; S, 4.93.

Found: C, 55.05; H, 4.77; Cl, 5.77; N, 10.51; S, 4.90.

[1205]

[Example 175]

4-[4-[[cis-2,6-Bis(ethoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1206]

^{1}H-NMR ($CDCl_3$) δ: 2.85-2.95(4H,m), 3.20-3.40(4H,m), 3.63(6H,s), 4.25-4.35(2H,m), 7.45-7.50(4H,m), 7.55-7.65(3H,m), 7.70-7.80(1H,m), 7.90-7.95(3H,m), 8.25-8.35(3H,m).

MS (FAB) m/z: 652 [$(M+H)^+$, Cl^{35}], 654 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{32}H_{30}ClN_3O_8S \cdot 2.3H_2O$

Calculated: C, 55.42; H, 5.03; Cl, 5.11; N, 6.06; S, 4.62.

Found: C, 55.50; H, 4.93; Cl, 5.12; N, 5.89; S, 4.54.

[1207]

[Example 176]

trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 105, the title compound was obtained using trans-2,6-bis(carbamoylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a raw material.

[1208]

^{1}H-NMR (DMSO-d_6) δ: 2.50-2.60(4H,m), 3.20-3.30(4H,m), 4.15-4.25(2H,m), 6.87(2H,br s), 7.40(2H,br s), 7.62(2H,d,J=8.8Hz), 7.72(1H,d,J=8.3Hz), 7.82(1H,d,J=8.8Hz), 8.02(2H,d,J=8.3Hz), 8.16(1H,d,J=8.8Hz), 8.20-8.40(4H,m), 8.51(1H,s), 8.90-9.00(2H,m).

MS (FAB) m/z: 606 [$(M+H)^+$, Cl^{35}], 608 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{30}H_{28}ClN_5O_5S \cdot 1.2HCl \cdot 3H_2O$

Calculated: C, 51.19; H, 5.04; Cl, 11.08; N, 9.95; S, 4.56.

Found: C, 51.10; H, 4.97; Cl, 11.17; N, 9.71; S, 4.64.

[1209]

[Example 177]

4-[4-[[trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1210]

^{1}H-NMR (DMSO-d_6) δ: 2.55-2.65(2H,m), 2.65-2.80(2H,m), 3.20-3.60(4H,m), 4.25-4.35(2H,m), 4.90-5.00(1H,m), 6.98(2H,br), 7.48(2H,br), 7.55-7.65(2H,m), 7.80-8.00(6H,m), 8.20-8.40(5H,m), 8.60(1H,s).

MS (FAB) m/z: 622 [$(M+H)^+$, Cl^{35}], 624 [$(M+H)^+$, Cl^{37}].

[1211]

[Example 178]

trans-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 3, the title compound was obtained.

[1212]

^{1}H-NMR (DMSO-d_6) δ: 2.50-2.75(4H,m), 3.25-3.45(4H,m), 4.15-4.25(2H,m), 7.52(2H,d,J=8.3Hz), 7.70-7.75(3H,m), 7.80-7.85(3H,m), 8.16(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.51(1H,s), 8.60-8.70(2H,m), 12.32(2H,s).

MS (FAB) m/z: 608 [$(M+H)^+$, Cl^{35}], 610 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{30}H_{26}ClN_3O_7S \cdot 0.2HCl \cdot 0.5H_2O$

Calculated: C, 57.71; H, 4.39; Cl, 6.81; N, 6.73; S, 5.14.

Found: C, 57.78; H, 4.35; Cl, 6.73; N, 6.68; S, 5.11.

[1213]

[Example 179]

trans-2,6-Bis(2-hydroxyethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (40 l), trans-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine (269 mg) was suspended, followed by the addition of N,N-diisopropylethylamine (480 µl) and 1-benzotriazolyloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (672 mg) under ice cooling. The resulting mixture was stirred for 3.5 hours at room temperature. Under ice cooling, sodium borohydride (297 mg) was added and the resulting mixture was stirred for 15 hours at room temperature. After ice cooling, the reaction mixture was added with water and ethyl acetate and the organic layer was collected. The resulting organic layer was washed with saturated saline and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (4% methanol - dichloromethane), followed by dissolution in tetrahydrofuran. Saturated methanol hydrochloride was added to the resulting solution and the resulting mixture was concentrated to dryness. Ethyl acetate was then added to the residue to crystallize the

same, whereby the title compound was obtained.

[1214]

^{1}H-NMR (DMSO-d_6) δ: 1.60-1.80(2H,m), 1.80-1.95(2H,m), 3.20-3.40(6H,m), 3.95-4.05(2H,m), 7.59(2H,d,J=8.3Hz), 7.70-7.75(3H,m), 7.80-7.90(31H,m), 7.99(2H,d,J=8.3Hz), 8.17(1H,d,J=8.8Hz), 8.20-8.30(4H,m), 8.54(1H,s), 8.85-8.95(2H,m).

HRMS (FAB) m/z: 580.1633 $(M+H)^+$ (calcd for $C_{30}H_{30}ClN_3O_5S$ 580.1673).

[1215]

[Example 180]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

In the same manner as in Example 4, the title compound was obtained.

[1216]

^{1}H-NMR (DMSO-d_6) δ: 2.74(3H,s), 2.99-3.81(8H,br), 7.71(1H,s), 7.33(1H,dd,J=8.8,2.0Hz), 7.51(1H,d,J=8.8Hz), 7.58(2H,d,J=8.3Hz), 7.79(1H,d,J=2.0Hz), 8.00(2H,d,J=8.3Hz), 8.77-8.84(1H,m), 8.79(1H,d,J=6.3Hz), 12.50(1H,s).

MS (FAB) m/z: 495 [$(M+H)^+$, Cl^{35}], 497 [$(M+H)^+$, Cl^{37}].

Elementary analysis for $C_{25}H_{23}ClN_4O_3S \cdot 0.9HCl \cdot H_2O$

Calculated: C, 55.01; H, 4.78; Cl, 12.34; N, 10.26; S, 5.87.

Found: C, 54.99; H, 5.01; Cl, 12.12; N, 10.03; S, 5.88.

[1217]

[Example 181]

4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example 6, the title compound was obtained.

[1218]

MS (FAB) m/z: 511 [$(M+H)^+$, Cl^{35}], 513 [$(M+H)^+$, Cl^{37}].

^{1}H-NMR (DMSO-d_6) δ: 2.95-3.18(4H,br), 3.37-3.81(4H,br), 7.03(1H,s), 7.34(1H,dd,J=8.8,2.0Hz), 7.47(2H,d,J=8.3Hz), 7.51(1H,d,J=8.8Hz), 7.66(1H,dd,J=6.8,2.9Hz), 7.79(1H,s), 7.80(2H,d,J=8.3Hz), 7.91(1H,d,J=2.9Hz), 8.30(1H,d,J=6.8Hz), 12.42(1H,s).

Elementary analysis for $C_{25}H_{23}ClN_4O_4S \cdot 0.8H_2O$

Calculated: C, 57.15; H, 4.72; Cl, 6.75; N, 10.66; S, 6.10.

Found: C, 57.22; H, 4.64; Cl, 7.04; N, 10.42; S, 6.17.

[1219]

[Test 1] Measurement of FXa inhibitory action (IC_{50})

In a 96-well microtiter plate, 10 µl of a sample solution, 40 µl of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 µl of 0.05 U/ml human FXa ("Cosmobio-ERL HFXa-1011", dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40 ml of 750 µM S2222 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each

sample was determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC_{50}) was determined.

[1220]

Inhibitory ratio (%) = (1 - OD of sample ÷ OD of control) x 100

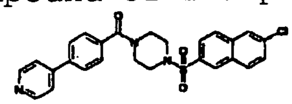
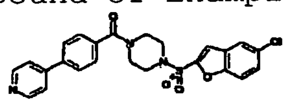
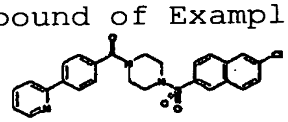
[1221]

(Results)

The compound of the formula (I) having, in the structure thereof, an unsubstituted pyridylphenyl group as the group Q^1-Q^2- and a chloronaphthyl or chlorobenzofuranyl group as the group Q^A is found to have FXa activity 50% inhibitory concentration (IC_{50}) of 100 nM or greater (refer to Table 1).

[1222]

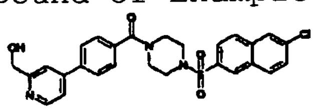
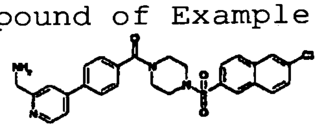
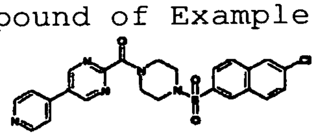
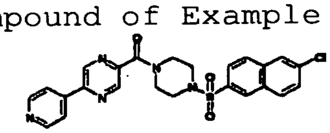
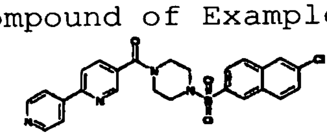
[Table 1]

Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 1 	123
Compound of Example 85 	1000
Compound of Example 17 	180

The compound similar to the compound of Example 1 except for having a substituted pyridylphenyl group, pyridylpyrimidinyl group, pyridylpyrazyl group or pyridylpyridyl group instead of the pyridylphenyl group is found to have FXa inhibitory action improved by several times as much as that of the compound of Example 1 (refer to Table 2).

[1223]

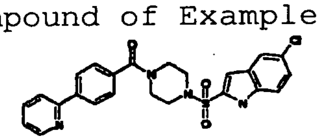
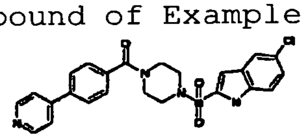
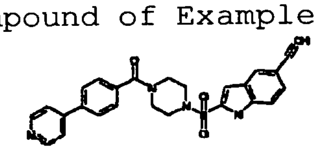
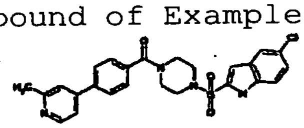
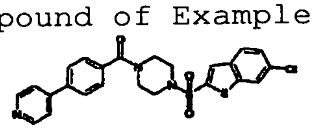
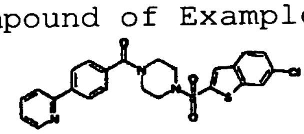
[Table 2]

Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 152 	38
Compound of Example 155 	28
Compound of Example 123 	23
Compound of Example 137 	60
Compound of Example 4 	54

The compound similar to that of Example 1 except for having, as the group Q^A, a 6-chlorobenzothienyl group, 5-ethynylindolyl group or 5-chloroindolyl group instead of chloronaphthyl group is found to be particularly excellent in FXa inhibitory action (refer to Table 3).

[1224]

[Table 3]

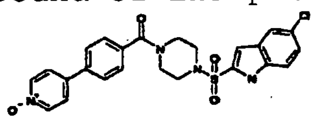
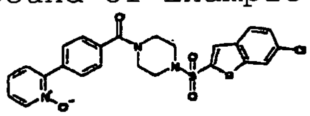
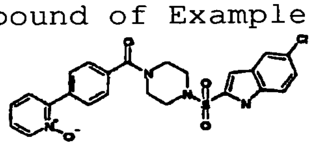
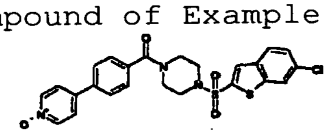
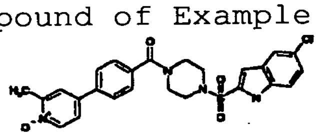
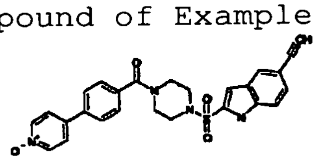
Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 90 	16
Compound of Example 101 	9.5
Compound of Example 103 	27
Compound of Example 180 	15
Compound of Example 97 	82
Compound of Example 98 	125

The compound having, as the group Q^1-Q^2-, a pyridylphenyl group is found to show a drastic improvement in the FXa

inhibitory action when the nitrogen atom on the pyridine ring has been converted into N-oxide and the group Q^A represents a 6-chlorobenzothienyl group, 5-ethynylindolyl group or 5-chloroindolyl group (refer to Table 4).

[1225]

[Table 4]

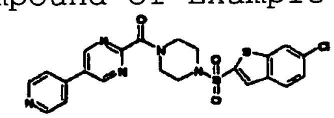
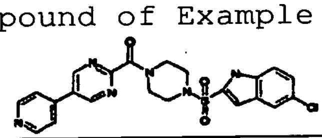
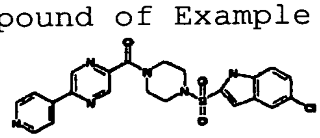
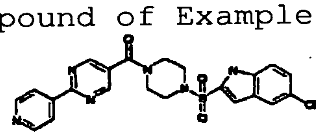
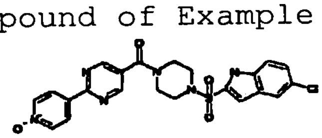
Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 107 	4.7
Compound of Example 117 	10.5
Compound of Example 109 	6.9
Compound of Example 116 	8.6
Compound of Example 181 	2.9
Compound of Example 120 	14

The compound having, as the group Q^1-Q^2-, a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl group and, as

the group Q^A, a 6-chlorobenzothienyl, 5-ethynylindolyl or 5-chloroindolyl group is found to be markedly excellent in FXa inhibitory action (refer to Table 5).

[1226]

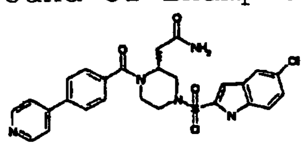
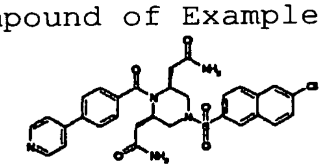
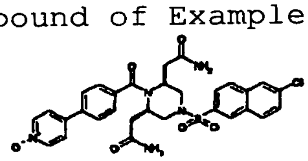
[Table 5]

Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 132 	5.6
Compound of Example 105 	2.4
Compound of Example 138 	5
Compound of Example 131 	19
Compound of Example 135 	14

The compound having one or two substituents introduced in the group Q^3 is found to exhibit strong FXa inhibitory activity (refer to Table 6).

[1227]

[Table 6]

Sample compound	Sample concentration (nM) at which 50% of FXa activity is inhibited
Compound of Example 130 	3.6
Compound of Example 173 	10
Compound of Example 174 	20

[1228]

[Test 2] Measurement of thrombin inhibitory action (IC_{50})

In each of a 96-well microtiter plate, 10 µl of a sample solution, 40 µl of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 µl of 4 U/ml human thrombin (Sigma Chemical, dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40 µl of 500 µM S2266 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each

sample was determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC_{50}) was found.

[1229]

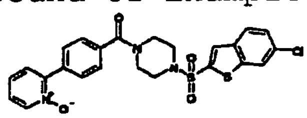
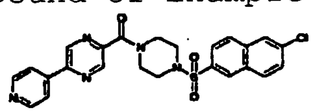
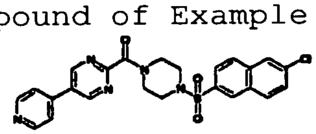
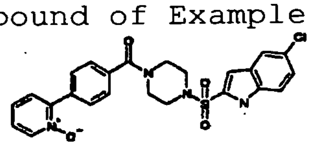
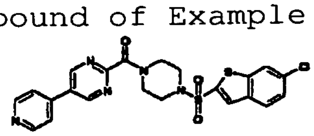
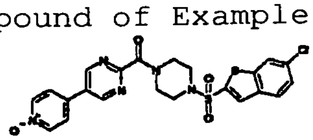
Inhibitory ratio (%) = (1 - OD of sample ÷ OD of control) x 100

[1230]

The compound having, in the structure thereof, a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl, a 6-chlorobenzothienyl group, a 5-ethynylindolyl group or a 5-chloroindolyl group; or the compound having, in the structure thereof, a 6-chlorobenzothienyl, 5-ethynylindolyl or 5-chloroindolyl group, in addition to a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl is found to exhibit markedly low thrombin-activity inhibitory action compared with excellent Xa inhibitory action (refer to Tables 7 and 8).

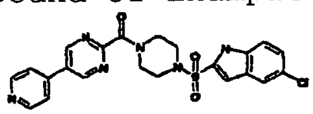
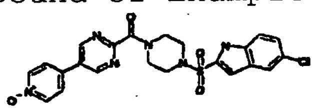
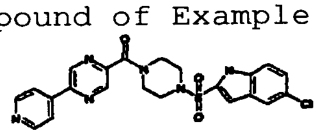
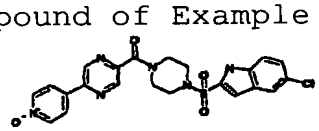
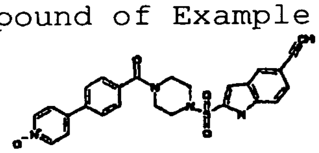
[1231]

[Table 7]

Sample compound	Sample concentration (nM) at which 50% of thrombin activity is inhibited
Compound of Example 117 	4100
Compound of Example 137 	4100
Compound of Example 123 	16000
Compound of Example 109 	1550
Compound of Example 132 	> 100000
Compound of Example 133 	7700

[1232]

[Table 8]

Sample compound	Sample concentration (nM) at which 50% of thrombin action is inhibited
Compound of Example 105 	19000
Compound of Example 134 	10200
Compound of Example 138 	5900
Compound of Example 140 	1370
Compound of Example 103 	2220

[1233]

[Test 3] Test of oral administration

1) Method

A sample was dissolved or suspended in a 0.5% (w/v) methyl cellulose solution and the resulting solution or suspension was

orally administered (10 ml/kg) to a 8 to 11 week-old rat (Wistar male rat (Nippon SLC Co., Ltd.)) which had been fasted overnight. After administration of the sample, the blood to which 1/10 part by weight of 3.13% (w/v) sodium citrate had been added was collected from the cervical vein under anesthesia with halothane. The rat was awakened except during the blood collection. Feeding was re-started 6 hours after the blood collection. From each blood sample, the plasma was separated by centrifugal separation and anti-FXa activity in the blood and prothrombin time extending action were measured.

[1234]

2) Measuring method

2-1) Measurement of anti-FXa activity in the plasma

In a 96-well plate, 5 µl of the plasma was poured in portions, followed by the addition of 55 µl of a 8:1:2 mixture of 100 mM tris · 200 mM sodium chloride · 0.2% BSA (pH 7.4) buffer, water and 0.1 U/ml human Factor Xa solution (dissolved in and diluted with a measuring buffer) and 40 µl of 750 µM S-2222. After stirring for 10 seconds in a plate mixer, an increase (mOD/min) of the absorbance at 405 nm was measured at room temperature. The inhibitory ratio was calculated as follows:

[1235]

An inhibitory ratio (%) = (1 - OD of sample ÷ OD of control on average relative to blood-collecting time of sample) x 100

[1236]

2-2) Measurement of coagulation extending action in oral administration (measurement of prothrombin time)

To 20 µl of the plasma, 40 µl of cynplastin (Organon Teknika/USA) was added and the coagulation time was measured. The ratio of the prothrombin time after the administration of the sample relative to the prothrombin time before the administration of the sample was designated as an index of the coagulation extending action.

[1237]

3) Results

The compound of Example 60 showed an anti-FXa activity of 70% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the prothrombin time by 1.18 times.

[Document Name] ABSTRACT

[Abstract]

[Problem] To provide, as an excellent anticoagulant, a novel sulfonyl derivative or salt thereof, or a solvate thereof which has strong FXa inhibitory action, exhibits prompt, sufficient and long-lasting anti-thrombus effects even by the oral administration and has reduced side effects.

[Means for the Solution] A sulfonyl derivative represented by the following formula (I):

[Chemical formula 1]

$$Q^1-Q^2-T^1-Q^3-SO_2-Q^A \qquad (I)$$

[wherein, Q^1 represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent,

Q^2 represents a single bond, an oxygen atom, a sulfur atom, a linear or branched C_{1-6} alkylene group, etc.,

Q^A represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, etc. and

T^1 represents a carbonyl group, etc., or salt thereof, or solvate thereof.

[Selected Figure of Drawings] None

【Document Name】 Data of Correction ex officio
【Corrected Document】 Patent for Application

〈Recognized Information/Additional Information〉
【Applicant】 PETITIONER
【Identification Number】 000002831
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【Name】 DAIICHI PHARMACEUTICAL CO., LTD.

10-244175

PERSONAL HISTORY OF APPLICANT

Identification Number : [000002831]

1. Date of change August 28, 1990
   [Reason of change] New Registration
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